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LECTURES

ON

PHARMACOLOGY

FOR

PRACTITIONERS AND STUDENTS.

BY

DR. C.ar BINZ, 1832 -

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We now pass on to the consideration of another group of remedies, namely, those containing TANNIC ACID. Acidum tannicum, tannin, occurs as a white or yellowish amorphous powder, or as thin, glistening, almost colourless scales. It is soluble in an equal weight of water, and in two parts of alcohol, but insoluble in pure ether. The solutions have an acid reaction, an astringent taste, and form a bluish-black precipitate with the persalts of iron.

Tannic acid is obtained from oak galls, gallæ, especially from those found on *Quercus lusitanica*, var. *infectoria*, a shrub or small tree growing in Asia Minor. Galls are round excrescences on the young shoots, caused by the puncture of the gall-insect, *Cynips gallæ-tinctoriæ*. In

spring, when the leaves are in bud, the female with her ovipositor punctures the tender cellular tissue, and there deposits one or more eggs. The irritation of this causes a great enlargement of the leaf bud, forming an excrescence about 25 mm. in diameter, in which the larva rests, and from which the insect escapes as soon as it has completed its transformation, by cutting out a circular passage about 3 mm. wide. Tannic acid is meanwhile developed in the substance of the gall in considerable quantity, forming as much as 70 per cent. of the whole. These bodies are therefore the chief source from which tannic acid is obtained.

The following chemical properties of tannic acid are important from a therapeutic point of view: its formula is $C_{14}H_{10}O_9$ or anhydrous digallic acid,

$$2C_7H_6O_5 \text{ (gallic acid)} - H_2O = C_{14}H_{10}O_9 \text{ (tannic acid)}.$$

It is a weak acid, but nevertheless it decomposes carbonates; its salts are all amorphous, and rarely have a constant composition. The commercial acid usually contains considerable quantities of gallic acid and sugar, both of which are derived from the galls. The composition of gallic acid—$C_6H_2.(OH)_3.COOH$—indicates that tannic acid is a derivative of benzene.

The oak galls of Asia Minor, with their astringent taste, were well known to the disciples of Hippocrates, and were employed medicinally in the same way as we now use their chief constituent. It was not, however, until the present day that tannic acid was thoroughly investigated, either from a chemical or a pharmacological point of view. It was noticed that substances which were used in the manufacture of leather, had an astringent and styptic action on mucous membranes and ulcerated surfaces. This was proved to depend upon the property which tannic acid possesses of yielding with albumen, and especially with gelatine, a dense insoluble precipitate.

I add a few drops of a solution of tannin to this solution of gelatine in warm water. There is an immediate precipitate; the affinity between the two substances is, in fact, so great that by putting a strip of gelatine into a stronger solution of tannin, we can abstract the whole of the latter.

The precipitate is insoluble in mineral acids, and, as you see, on adding hydrochloric acid it becomes denser than before. This fact appears to me sufficiently to explain the local action of tannin; for, when applied to mucous membranes or to ulcers, it must everywhere meet with tissues containing albumen, fibrin, and gelatine. This action of tannin, which I here demonstrate to you in the test tube, produces a kind of coagulation, an effect also produced in the manufacture of leather by tanning, the skins being thereby rendered firm and capable of resisting moisture and decomposition; this action, when exerted on mucous membranes and ulcers causes a contraction of all the tissue elements.

But it has also been supposed that tannic acid acts on distant organs through the circulation. I will merely mention one example of this, namely the recommendation by Frerichs of the employment of tannic acid in cases of Bright's disease, where, he maintains, it acts beneficially by restoring the normal tone of the renal capillaries, and also by diminishing the loss of albumen.[1]

After administering on an average 0·24 grammes (3·6 grains) of tannin three times a day, together with extract of aloes, the amount of albumen in the urine was uniformly decreased, although it rarely disappeared entirely. The possibility of such a remote action, however, has been much disputed. I will now show to you some experiments bearing upon this.

The precipitate of albuminate of tannin is dissolved, as I here show you, in alkaline carbonates; tannic acid can therefore be absorbed from the intestinal canal without causing coagulation in the vessels, and circulates everywhere as an alkaline salt. This alkaline tannate, however, has the same action and the characteristic astringent taste peculiar to tannin itself. Whether we are justified from this in drawing the conclusion that the salt has an astringent action upon other tissues besides the organ of taste, is open to question. It could only be possible where the tissue has an acid reaction and is consequently able to liberate the tannic acid from the alkali. In such a case we

[1] Frerichs, 'Die Bright'sche Nierenkrankheit und deren Behandlung,' 1851, S. 225; Pribram, 'Wien. med. Wochenschr.,' 1883, S. 103.

can imagine that a continuous, although slight astringent action might be produced.

In order to justify such a supposition, however, we must first prove that tannic acid reaches any distant organ such as the kidneys, without undergoing decomposition. It was formerly supposed that tannic acid on coming in contact with blood and tissues was completely decomposed and oxidized, chiefly into gallic acid and a little pyrogallol.[1] But GALLIC acid, as you can see here in the test tube, does not precipitate albumen or gelatine, that is to say, has not that property on which the astringent action of tannic acid appears to depend; it is obvious that we have great reason to doubt the possibility of any effect of this kind being produced through the medium of the circulation.[2]

Lewin and Ribbert have shown by experiments upon rabbits that a portion of the tannic acid does actually reappear in the urine. Experiments upon dogs[3] produced the following results:—After administering to them free tannic acid, gallic acid appeared in the urine, and occasionally a trace of tannic acid was found; whilst after giving sodium tannate, the urine was found to contain tannic acid, and only a trifling quantity of gallic acid. Pyrogallic acid was not found. In experiments upon healthy men there was no blue-black colouration of the urine on the addition of ferric salts, even after considerable quantities of the drug had been administered. It was, therefore, concluded that tannic acid, in man, is either not excreted by the kidneys, or is entirely decomposed in the body. Other experiments on human beings have given almost exactly the same results.[4]

Consequently, the presence of tannin in the urine in the experiments on animals above referred to, has only a theoretical interest. In fact, in a case of nephritis[5] in the

[1] Wöhler and Frerichs, 'Anal. d. Chem. u. Pharm.,' 1848, Bd. lxv, S. 339; O. Schultzen, 'Arch. f. Anat. u. Physiol.,' 1863, S. 25.

[2] C. Hennig, "Ueber therap. Verwendung vegetabil. Adstringentien," 'Arch. f. physiol. Heilkunde,' 1853, Bd. xii, S. 613.

[3] Ralph Stockman, 'Brit. Med. Journ.,' December 4th, 1886.

[4] C. Th. Mörner, 'Zeitschr. f. physiol. Chemie,' 1892, Bd. xvi, S. 265.

[5] G. Lewald, "Ueber die Ausscheidung von Arzneimitteln aus dem

human subject, the diminution in the amount of albumen in the urine after the administration of tannic acid was quite insignificant, and probably all authorities now regard tannin and its preparations as useless in chronic Bright's disease,[1] although this disease appears to offer a peculiar field for its action.

Still less reason is there for believing the assertion so frequently made, that acting through the blood, tannic acid can check hæmorrhage from bleeding vessels. An alkaline tannate causes no coagulation of albumen in alkaline blood, it causes no contraction of the blood-vessels, and it has no action upon the injured and bleeding part. Consequently, when it is assumed that the hæmorrhage has ceased after the administration by the mouth of a few grains of tannin, there has probably been some confusion in the observer's mind as to cause and effect.

The action of tannic acid upon the INTESTINES is of some importance. Hennig found, as Mitscherlich had done previously, that a dose of 1·9 gramme (about 30 grains) did not diminish the quantity of fæces, but made them drier, and deprived them of their peculiar odour. He came to the conclusion, therefore, that tannic acid does not lessen the peristaltic movements, but merely checks the secretion of the glands. We must also conclude, as the fæcal odour is diminished, that tannin, when given in the above large doses, modifies some of the changes which usually take place in the intestine. Hennig injected some tannin dissolved in a little distilled water, into the small intestine of a decapitated animal, after all peristaltic movement had ceased. This was followed by a somewhat rapid contraction of the part, the bowel being contracted for some time, and certainly more strongly than when water alone was injected. We may consider, therefore, that tannin in the human subject acts locally along the whole course of the intestine, the action continuing for some time on its walls. This local

Organismus, insbesondere über die durch mineralische und vegetabilische Adstringentien durch die Nieren und ihren Einfluss auf die Thätigkeit derselben," 'Jahresber. d. Schles. Ges. Med. Sitzung.,' September 13th, 1861, S. 236.

[1] Ziemssen, 'Verhandl. des. g. med. Congresses in Wien,' 1890, S. 172.

action causing an astringent effect, and diminishing secretion from a part, is often advantageously employed in affections of the mucous membrane of the pharynx, of the respiratory passages, the rectum, the urethra, and the vagina.

Tannic acid is an antiseptic and deodoriser. It preserves liquids which are liable to decompose, and checks decomposition when it has already begun. This is due, as may be easily seen with the microscope, to its poisonous action upon bacteria; the micro-organisms become opaque, and are destroyed. Tannic acid is, nevertheless, inferior in this respect to a large number of other substances, and we must employ a much stronger solution of it than of the others if we wish to obtain the same results. For this reason it is seldom included among the usual antiseptic agents, and no satisfactory explanation has hitherto been given why it acts as a deodoriser and, in a few minutes, removes objectionable smells from decomposing fluids.

Tannic acid is NOT POISONOUS in the ordinary sense of the term, it does not affect the nervous system. Natural digestion is not deranged by moderate doses of tannin; on the contrary, the drug often seems to improve the digestion by gently stimulating the walls of the stomach and intestines. When too large a dose is given, poisonous effects may be produced from direct irritation of the stomach and bowels. The usual dose is from 0·1 to 0·3 gramme (1½ to 4½ grains).

Some remarkable idiosyncrasies with regard to tannin have been reported.[1] Painting the pharynx with a 7 per cent. solution, on one occasion, was followed by considerable swelling of the mucous membrane, by cutaneous urticaria, and stupor.

Tannin must not be prescribed with metallic salts, with alkaloids, or with substances containing gum or albumen, as it forms compounds with these which are either not readily soluble or are quite insoluble. Of the officinal alkaloids, morphine may be excepted, as it is not readily precipitated by tannin. The other usual alkaloids are, however, so quickly precipitated by it that in cases of poisoning, when any one of them has been recently swallowed, the first thing

[1] V. Lange, 'Deutsche med. Wochenschr.,' 1880, S. 11; Jürgensmeyer, ibid., 1890, S. 779.

to be done is to administer as quickly as possible a solution of tannin as an antidote.

A solution of about 1 gramme (15 grains) of tannic acid in lukewarm water is also given when some METALLIC POISON is supposed to be still in the stomach, on the ground that a compound is formed which is either completely insoluble or not readily soluble.

An AQUEOUS SOLUTION of tannic acid soon undergoes changes, as you see is the case in this 5 per cent. solution, which was prepared three weeks ago, and then covered up and kept in a warm room. It is brown, and there is a precipitate at the bottom a finger's breadth thick, which, on microscopical examination, proves to consist entirely of hypomycetes. Naturally the growth must have produced some change in the acid, and this is seen to be the case on adding the solution to a solution of gelatine. No trace of a precipitate is formed, and the tannic acid has therefore disappeared. As ferric chloride, however, produces a bluish-black precipitate when added to the solution, the tannic acid has been converted into gallic acid. Such a solution is no longer of any use for astringent purposes.

All that I have said so far, refers to the tannic acid obtained from galls. Tannic acid or tannin is a general name for many bodies which possess the chief properties of gallo-tannic acid, but are not identical with it. For example, the tannic acid of galls gives a *bluish-black* precipitate with ferric chloride, the tannic acid of certain other drugs, to be referred to presently, gives a dark *green* precipitate. Gallo-tannic acid, when submitted to a dry heat is converted into pyrogallol $C_6H_3(OH)_3$, other tannic acids are converted into pyrocatechine $C_6H_4(OH)_2$. The other officinal substances, besides galls, of which the principal constituent is tannic acid, are the following:

CORTEX QUERCÛS, oak bark, the young bark of *Quercus robur*, which has a shining silvery or ash-grey colour, variegated with brown. Its decoction is employed for fomentations and baths.

CATECHU is an extract prepared in India from the leaves of *Uncaria gambir*, and from the wood of *Acacia catechu*. It has a bitter, astringent taste, and a sweet after-taste. Its

principal ingredients are catechu and catechu-tannic acid; the former is a crystalline substance, and, when heated, is converted into the acid.

RADIX RHATANIÆ, rhatany, is the root of *Krameria triandra*, a shrub which grows in Peru and the neighbouring countries. As much as 42 per cent. of a tannic acid which gives a green precipitate with ferric chloride has been obtained from it.

These drugs have not been closely investigated from a pharmacological point of view. As they contain a different kind of tannic acid, as well as other substances about the nature of which we know little, it is quite possible that physicians are correct in stating that these drugs, their extracts and tinctures, are for many purposes more useful than the pure gallo-tannic acid. This may also arise from the presence of various kinds of extractive matter, which envelope the tannic acid and impede its absorption, and so allow it to pass lower down the intestinal canal.

FOLIA UVÆ URSI, bearberry leaves, are included amongst the drugs containing tannic acid, but their principal constituent is undoubtedly arbutine, which is allied to hydroquinone, and therefore belongs to a group which I shall discuss later on.

The SIMPLE BITTERS are closely related, as regards their specific properties and actions, to the tannic acid group. In former times the remedies belonging to this group were said to act by increasing the "tone" of the mucous membrane of the alimentary canal, and were used simply for this purpose.

Among this group we may include the bitter constituents of *Menyanthes trifoliata*, *Gentiana lutea*, *Erythræa centaurium*, *Cnicus benedictus*, *Quassia amara*, *Jateorrhiza calumba*, *Cetraria islandica*, and *Croton eluteria*. I have only mentioned those which are still officinal in Germany, the greater

number of those formerly in use having either become obsolete, or being now simply used as ingredients of some popular or secret remedy. The bitter principles of quinine, strychnine, aloes, and rhubarb may also in a certain sense be included in this group, but as these remedies possess other more important properties, the consideration of their action will be taken at some more appropriate time. Finally, I may also mention that a few of those plants from which the ethereal oils are derived, such as *Artemesia absinthium*, contain a considerable amount of bitter substances, and might also be included in the present group.

Practical experience in the therapeutic use of these bitter remedies again preceded the scientific investigation of their action; they belong to the most ancient and most widely used remedies. In all cases of simple dyspepsia, when the stomach is otherwise healthy, they are employed in order to stimulate the action of the peptic glands. The gaseous and acid eructations cease, the taste becomes normal, the fur disappears from the tongue, the appetite returns, and the general nutrition is improved.

Some recent investigations on the action of these bitters have been made.[1] Before administering the remedy, considerable labour was bestowed in determining—by the usual methods—the amount of gastric secretion, together with the change which took place, and the time occupied by the digestive process, both in healthy individuals and in patients suffering from disease. Corresponding investigations were then made as to the effect of the bitters, when given in the form of infusions. The results obtained from a large number of separate experiments on a variety of people were essentially as follows:—

The action of the various bitter herbs that were experimented with, viz. *Herba centaurii, Folia trifolii, Radii gentianæ, Lignum quassiæ, Herba absinthii*, is very similar. During fasting, whether the secretion of gastric juice at the time be normal in quantity or greater or less than normal, the administration of a bitter infusion immediately produces

[1] N. Reichmann, "Exper. Untersuch. über d. Einfluss der bittern Mittel auf die Function des ges. u. kr. Magens," 'Zeitschr. f. klin. Med.,' 1889, Bd. iii, S. 177.

a smaller amount of secretion than is the case when the same quantity of distilled water is taken. After the infusion has been absorbed from the stomach, the SECRETION OF GASTRIC JUICE IS INCREASED. If the bitter is taken at the same time as the food, its digestion in the stomach is impeded. W. Beaumont[1] in his classical work based on experiments on a Canadian beaver-trapper who had a gastric fistula, states that stimulating condiments instead of being harmless are actually prejudicial to the healthy stomach. "They can only be required and taken with benefit when the gastric apparatus is languid and relaxed, and requires stimulants to excite the tone and action of its vascular tissues." Beaumont referred more especially to mustard, but experience has taught us that the same is true of the simple bitters. If the effect is too strong or too frequently repeated, the stomach at last becomes permanently affected. Relaxation of the blood-vessels, hyperplasia of the mucous membrane, too great a secretion of mucus and too small a secretion of gastric juice, feeble peristalsis,—may all be set up by prolonged over-stimulation.

The beneficial effect of the simple bitters is not, however, confined to the stomach. The changes going on within the small intestine, where, according to the investigations of C. v. Noorden,[2] the absorption of nutritive material chiefly takes place, are also favourably influenced by bitters. This is borne out by the following experiments.

In the year 1856 the results of an investigation into the relative number of red and white blood-corpuscles in human beings were published.[3] These showed among other things that the administration of 30 drops of either Tinctura Myrrhæ (a gum-resinous exudation from the stem of *Balsamodendron myrrha*, an Arabian shrub belonging to the Nat. Ord. Burseraceæ), Tinctura Quininæ, Tinctura Amara,

[1] W. Beaumont, "Experiments and Observations on the Gastric Juice, and the Physiology of Digestion;" reprinted from the Plattsburg edition with notes by Andrew Coombe. Edinb., 1838, p. 258; see also R. Buchheim, 'Beiträge zur Arzneimittellehre,' 1849, S. 83.

[2] C. v. Noorden, 'Zeitschr. f. klin. Med.,' 1890, Bd. xvii, Ss. 17, 137, u. 514.

[3] E. Hirt, 'Arch. f. Anat. u. Physiol.,' 1856, S. 174.

or Tinctura Ferri Pomata, caused a visible increase in the number of white blood cells in a drop of blood taken from the finger. No attention was paid at the time to these experiments, but in 1874 I requested my pupils[1] to repeat them, and as they found the statements correct, to extend the investigation.

The effects of oil of turpentine, camphor, cymol, oil of valerian, oil of cinnamon, oil of fennel, cloves, white pepper, and tincture of orange, in increasing the number of white corpuscles, were also tested. In each experiment, five to fifteen drops of the oil were administered on a little sugar, and followed by a draught of water; the dose of camphor used was 0·25 gramme (about 4 grains). The normal number of leucocytes in the blood was first observed, and it was found on every occasion after the ethereal oils had been taken that there was a great increase, more than double their number appearing within ten minutes—a condition which lasted for over half an hour. After 25 drops of acetic ether had been given, the number was trebled.

This action takes place in the intestines, and does not result from the effect on the nervous centres, for after I had given Dr. H. Meyer subcutaneously a thoroughly effective dose of one of these oils, no increase at all took place in the number of the leucocytes.

The action of oil of peppermint is a remarkable exception, for when it is swallowed no change is observed in the number of leucocytes, or, if any, the number is rather diminished.

A further investigation[2] carried out on dogs confirmed what Hirt and I had observed in the case of human beings. The following were found to act very efficiently in the way above stated:—Many acid ethers of the methane

[1] Hugo Meyer, "Ueber den Einfluss einiger Stoffe auf die Zahl der farblosen Zellen im Kreislauf." Doctordissertation, 1874. This also contains Siegen's experiments. C. Binz, 'Archiv f. exper. Path. u. Pharmak.,' 1876, Bd. v, S. 122.

[2] T. Pohl, 'Arch. f. exper. Path. u. Pharmak.,' 1888, Bd. xxv, Ss. 51 and 31; Kunkel and Michelsoln, the Doctordissertation of the latter: "Ein Beitrag zur Lehre von den weissen Blutkörperchen," Würzburg, 1889.

series, eleven ethereal oils, piperine and strychnine, absinthine, quassine, extract of gentian and of centaury (*Erythrea centaurium*). Musk, about the action of which nothing definite had been learned previously from experimental investigation, also belongs to this group. The following, as had already been partly proved by Hirt and myself, were shown to be inefficacious, namely, alcohol, hydrochloric acid, sodium bicarbonate, caffeine, and quinine.

It has long been known that the number of leucocytes in the blood is distinctly increased after taking a fair amount of albuminous food, and that the blood in the intestinal veins of a dog is richer in leucocytes, during digestion, than that in the arteries. It has also been further shown that carbohydrates, fats, the various salts, water, and other non-albuminous constituents of our food do not produce this result. The medicinal substances above mentioned act, therefore, in the same direction as ordinary albuminous food. Both cause an INCREASED migration of the leucocytes from the intestinal glands into the veins.

The bearing of this upon the nutrition of the body is not quite clear, but the similarity of the effect produced by the above-mentioned chemical substances to that resulting from ordinary albuminous food, points to some increase taking place in the nutritive processes in the body. We must, however, bear in mind two important facts—first, that the white blood-corpuscles act as ferments,[1] and can bring about changes in the cells and fluids; and secondly, that some of their albumen exists in the form of peptone. The results of pharmacological investigations with regard to the action of BITTER and AROMATIC substances on digestion and nutrition, at all events, correspond with what has been accepted and proved by medical experience and custom.

The bitters belonging to this group produce very little effect upon the nervous centres, the heart or other organs. Only when they are present in large quantities in the alimentary canal, or pass into the circulation, do they

[1] Rossbach, 'Verhandl. d. Congr. f. innere Med.,' 1887, S. 209, "The leucocytes throughout the body contain a sugar-forming ferment, and their migration into the alimentary canal is one source of the ptyalin in the digestive fluids."

produce irritative or narcotic effects. As a rule, the bitter extracts are destitute of nitrogen; they differ, therefore, essentially as regards chemical composition from the true alkaloids.

The following substances furnish the chief simple bitters; FOLIA TRIFOLII FIBRINI, the leaves of *Menyanthes trifoliata*, buckbean, contains menyanthine—$C_{30}H_{46}O_{14}$—an amorphous mass which on heating with sulphuric acid is decomposed into sugar, a volatile oil—menyanthol, and water.

RADIX GENTIANÆ: gentian root, the dried root of *Gentiana lutea*, which grows on the mountain-chains of Central and Southern Europe. The root contains a crystalline substance, Gentio-picrine—$C_{20}H_{30}O_{12}$—which is a glucoside, that is to say it can be resolved into glucose, and another body termed gentio-genine.

HERBA CENTAURII, common centaury, contains the bitter substance erythrocentaurin, the composition of which is said to be $C_{27}H_{24}O_8$.

HERBA CARDUI BENEDICTI, blessed thistle, yields the bitter substance cnicine—$C_{14}H_{18}O_5$—or its polymeride—$C_{42}H_{54}O_{15}$.

LIGNUM QUASSIÆ, quassia wood, the wood of *Picræna excelsa*, contains the crystalline substance quassin—$C_{10}H_{12}O_3$. The wood and its extract are much used as bitters for medical purposes, and owing to its lower price and higher value as a bitter, it is sometimes employed by brewers as a substitute for hops. When given in the small doses generally prescribed, it only acts upon the stomach, but in large doses it acts as a narcotic. A child, four years old, suffering from thread-worms, had by mistake an enema of 180 c.cm. (about six ounces) of a "concentrated" hot infusion of quassia administered to it, which was wholly retained in the bowels: the child remained in a condition of profound narcosis for many hours, the respiration and heart's action being extremely feeble.[1] Another child died with symptoms of complete paralysis, after having an enema consisting of a decoction of 2 ounces quassia in a pint of water; the first symptoms of poisoning appeared within five minutes after the enema had been given.[2] According to recent investiga-

[1] T. Reckett, 'Lancet,' 1880, ii, p. 260.

[2] F. Venn, 'Univ. Med. Magaz.,' Philadelphia, 1895, vol. vii, p. 304.

tions,[1] tincture of quassia when taken in large doses for a considerable time by healthy men, acts on the lower portions of the alimentary canal. It produces copious pultaceous stools, and moreover gives rise to tenesmus and increased secretion from the mucous membrane of the rectum.

RADIX CALUMBA, Calumba root, the root of *Jateorrhiza calumba,* contains two crystalline bitter substances, calumbine—$C_{20}A_{22}O_7$—and berberine—$C_{20}H_{17}NO_4$. Schroff[2] gave a single dose of 0·1 gramme (1½ grains) of calumbine to a man, but it produced no effect beyond the bitter taste in the mouth. It diminishes putrefactive changes in the intestine, that is to say, it lessens the quantity of the ethyl-sulphuric acid in the urine, to which these give rise.[3] Berberine, which, as its formula shows, is a vegetable alkaloid, is a crystalline body and forms crystalline salts, usually of a yellow colour, which are more easily soluble in water than in dilute acids. The alkaloid derives its name from the *Berberis vulgaris,* which contains a considerable quantity of it. Several experimental investigations have been made with regard to the action of berberine upon human beings. All that can be said about it, however, is that it occurs as a bitter, together with a calumbine, in calumba root, and that when this root and its preparations are given in the usual doses, we need have no fear of poisonous effects. Diarrhœa and painful peristalsis would be the primary indications of any deleterious action.

LICHEN ISLANDICUS, Iceland moss. This lichen also grows in Germany. A decoction of one part in twenty of water forms, on cooling, a stiff jelly with a bitter taste. The latter depends upon a crystalline substance, cetrarine, $C_{18}H_{16}O_8$, which is of an acid character, and forms compounds with alkalies which are soluble in water, but which readily decompose both in solution and on exposure to air. When swallowed by animals, cetrarine causes vigorous peristaltic movements and marked hyperæmia of the stomach. If a large dose is given, similar effects are produced upon

[1] H. Schulze and G. Kaempfe, the Doctordissertation of the latter, Greifswald, 1885.

[2] Schroff, 'Lehrbuch der Pharmakologie,' 1869, S. 120.

[3] G. Gara, 'Ungar Arch. d. Med.,' 1893, Bd. ii, S. 322.

the intestine, and it may even give rise to diarrhœa.[1] Iceland moss also contains about 70 per cent. of starch, the presence of which causes a decoction to gelatinise on cooling.

Cortex Cascarillæ, Cascarilla bark, the dried bark of *Croton eluteria*, a shrub (Euphorbiaceæ) growing in the Bahama islands. It contains a bitter substance, Cascarilline, $C_{12}H_{18}O_4$, with about 1 per cent. of resin and starch. Hot infusions of it and other extracts are used to stimulate the activity of the stomach.

Cortex Condurango, Condurango bark, is a new remedy, which at first was much esteemed. The bark is obtained from *Gonolobus condurango*, an Asclepiadea in Ecuador. It has a somewhat bitter and rough taste.

It was first heard of in 1871 in connection with a popular remedy against cancer and syphilis, which was highly esteemed in Loxa, a province of Ecuador. The representative of the United States in Quito reported the matter to his government, who ordered a sample of the drug to be sent to Professor Bliss, of Georgetown, and directed him to test its medicinal powers. Twenty-five kilogrammes were sent a little later to the medical societies of London and Paris. In North America numerous patients were treated with the remedy, but the results obtained did not agree with all that was stated in the commercial advertisements. In the Middlesex Hospital,[2] in London, it appeared to have no action upon carcinoma, and in the Imperial Rudolf Hospital of Vienna no greater success was obtained, so that "the vaunted remedy for cancer died a natural death"[3] as early as the end of the year 1871. It was not quite dead, however, for two years afterwards N. Friedreich,[4] a clinical teacher at Heidelberg, reported a case of cancer of the stomach in a man aged fifty-four, who had been admitted into his hospital. All the diagnostic signs were present; the

[1] Kobert, 'Historische Studien a. d. Pharmak. Institut zu Dorpat,' 1890, ii, S. 43. Comprehensive reports on bitters in general.

[2] Hulke, 'Med. Times and Gaz.,' 1871, vol. ii, p. 556; Kumar, 'Wiener med. Wochenschr.,' 1872, S. 690.

[3] K. Schroff, "Condurango, Zusammenstellung der darüber erschienenen Nachrichten." A paper read before the Vienna Medical Society, 29th November, 1871.

[4] N. Friedreich, 'Berliner klin. Wochenschr.,' 1874, S. 1.

man had marked cachexia, and a nodular, hard, confluent tumour which was sensitive to the touch. On the 18th of February, 1873, the treatment of the patient commenced with a decoction of 15 grammes of the bark in 180 of water (about 4 drachms to 6 ounces), a tablespoonful being taken three times a day. A month later the tumour had to a great extent disappeared, and all the symptoms of the patient continued to improve, until he left the hospital on the 15th of June apparently cured. He has since had no symptoms of any return of the mischief. This rehabilitation of a drug which had been stigmatised somewhat hastily as a swindle, again led a number of physicians to try this new remedy, in the hope of curing this hitherto incurable disease.[1]

Our present knowledge of the action of the drug may be stated as follows :—It acts chiefly on the stomach. In some cases of supposed cancer the tumour has diminished or disappeared after its use, in other cases no change has taken place. Nausea, vomiting, and pain have very frequently been considerably relieved by the prolonged use of this bark. The appetite, the digestion, the general condition and weight of the patient have improved. Consequently the continuous use of the bark is indicated in all cases of cancerous disease of the digestive canal, as well as in other affections of these organs in which there is any suspicion of cancerous mischief. The earlier the remedy is exhibited the better is the chance of success. Only large doses are of any service, the decoction or extract of 7 or 8 grammes (about 100 to 120 grains) of the bark must be given daily.

H. Schulz administered the tincture to eight students. Each of them experienced, after two doses of thirty drops, an increased desire for food, and this could only be ascribed to the condurango, as there had been no alteration in their

[1] Among the various papers on this subject the following may be mentioned:—F. Riegel, 'Berlin. klin. Wochenschr.,' 1874, S. 429; Becker, ibid., 1877, S. 691; Rühle, 'Deutsche med. Wochenschr.,' 1877, S. 170; Drszeweczky and Erichsen, 'Petersb. med. Wochenschr.,' 1876, Nos. 2 and 3; J. V. Dietrich, ibid., 1878, S. 203; Alb. Hoffmann, "Klin. Beob. über d. Wirk. d. Condurangorinde bei Carcinom." Doctor-dissertation from H. Immermann's clinic, 1881; G. Kaempfe's Doctor-dissertation, loc. cit.

mode of living. This increase of appetite amounted to a very marked feeling of hunger before the mid-day meal. The digestion and evacuations remained normal.

We do not know the nature of the constitutent which produces this effect. It is not tannic acid, for a preparation which was found to be very efficacious in the hospital here, only contained a trace of this substance. The bark contains a considerable number of resinous bodies,[1] and when boiled with a little soda gives off a faint aromatic odour. The method of prescribing the drug is of considerable importance, if we wish to make certain of getting proper results; the decoction must be EXPRESSED FROM THE BARK WHILST HOT, in the same manner as, according to the German Pharmacopœia, all other decoctions should be prepared. It seems that the action of the drug depends upon the ingredients which are insoluble in water; thus Rühle says, "It is a dark brown somewhat turbid fluid; the taste, which is very little characteristic, is of a somewhat insipid, slightly bitter, and aromatic nature. I have frequently seen it dispensed as a light brown clear liquid which had very little taste and which produced no results after being administered."

The officinal VINUM CONDURANGO[2] is prepared by macerating one part of the cortex with ten parts of sherry and then subjecting it to pressure. A tablespoonful of this may be taken four times a day.

The EXTRACTUM CONDURANGO FLUIDUM is prepared by macerating the cortex with alcohol, water and glycerine. Two or three teaspoonsful may be taken daily.

The alkaline carbonates, although they differ so much chemically from menyanthine, gentio-picrine, &c., have a very

[1] G. Jukna, in Kobert's 'Arbeiten a. d. Pharmakol. Inst. zu Dorpat,' 1890, iv, S. 81.

[2] Wilhelmy, 'Berl. klin. Wochenschr.,' 1888, S. 482.

similar action upon the stomach and upon the digestive process, to that of the vegetable bitters. I mean, of course, when they are administered in moderate or small quantities, for when given in large doses they act like all other alkalies upon the animal membranes,—irritating, disintegrating, dissolving, and destroying them. We will first take into consideration the best known member of the group, sodium carbonate—$Na_2CO_3 + 10H_2O$,—and I will assume that you are fully acquainted with the chemical relations of this elementary compound.

Sodium carbonate acts as an ANTACID in the stomach. It is usually prescribed under the supposition that the alkali combines with, and neutralises the effects of any foreign and noxious acids, such as butyric acid, &c., which may have been formed during morbid changes in the digestive processes, and that heartburn, flatulent eructations, and loss of appetite cease, the cause having been neutralised or removed.

The explanation, however, is not quite so simple. If this were the case, it would always be possible completely to neutralise these acids by giving large doses of sodium carbonate or bicarbonate. But this is quite impracticable. Very shortly after the existing acids have been neutralised they reappear in still larger quantities, and still larger doses of the alkali must be administered, and even then the heartburn only gradually disappears. In many cases, indeed, the formation of these acids is in no degree lessened by the administration of an alkali; a remedy of an opposite nature is required, namely hydrochloric acid, a few doses of which will effect what the antacid failed to do. The hydrochloric acid stops the further development of these noxious acids. This may be rendered somewhat clearer by reference to certain chemical facts.

If, in the laboratory, we wish to prepare butyric acid from sugar, we add to it, in addition to tartaric acid, putrid cheese, which, as is well known, contains the *Bacilli butyrici* or bacilli of butyric acid. These micro-organisms under the influence of warmth begin to increase, transforming the sugar first into lactic acid and then into butyric acid. So soon as these acids are present, in a free state, in the solution

they paralyse the micro-organisms, and cut short their further development. To prevent this we add at the commencement of the experiment some alkali (chalk) in excess, to combine with the acids and so allow the action of the micro-organisms to go on undisturbed.

The same effect is also produced in the stomach in dyspepsia. Any alkalies which may be administered simply have a favourable influence upon the growth of the butyric acid bacilli. There must, therefore, be some other reason why the abnormal fermentation set up by these micro-organisms is, in the slighter cases, checked by means of these alkalies.

From the experiments of Blondlot, Frerichs, and others, the reason appears to be that the alkalies when given in moderate doses act as stimulants to the glands. The alkaline fluid is absorbed almost immediately, but the secretion of normal gastric juice continues for a considerable time. Blondlot gave a dog some meat on which a little soda was sprinkled, and found that the first 40 to 50 grammes of the fluid, which passed from a gastric fistula, were either neutral or slightly alkaline, and that afterwards the acid gastric juice was secreted in exceptionally large quantity.[1]

E. Brücke[2] neutralised the surface of the gastric mucous membrane with magnesia usta, and then chopped it up with water. After standing for some time, the fluid again had an acid reaction.

The acid gastric juice is, however, as W. Beaumont has already proved, a good antiseptic. It therefore stops the development of the bacilli causing butyric acid and other fermentations, and so puts an end to the abnormal changes which are going on in the contents of the stomach.

Sodium carbonate does not, therefore, act therapeutically as an antaacid, but rather as a stimulant to the secretion of acid. The effect being limited to the secretion of NORMAL gastric juice, of course the free abnormal acids are at first neutralised by it, and so the heartburn, eructations, and other symptoms are immediately, though only temporarily, relieved.

[1] Heidenhain, 'Handbuch d. Physiol.,' 1880, Bd. v, Abt. 1, S. 115; W. Jaworski, 'Zeitschr. f. Biol.,' 1883, Bd. xix, S. 397.

[2] E. Brücke, see Landois, 'Lehrbuch d. Physiol.,' 1883, S. 307.

The alkalies also render less viscid the mucus which, in cases of dyspepsia, is secreted in increased quantity, and, accumulating on the surface of the mucous membrane, interferes with the intimate mixture of the gastric juice with the contents of the stomach. Again, the action of the alkaline carbonates upon the gastric glands increases the secretion of free hydrochloric acid, which acting on the carbonates, liberates the carbonic acid gas, and this, in some way, promotes absorption by the intestines, though how or why we are unable to say. Possibly the sodium chloride which is formed may tend to restore the organ to a normal condition, for we know from experience that small quantities of this salt act beneficially upon the normal digestion, though as to its mode of action we are also still somewhat in the dark.

Another observation[1] bearing on the subject may be here referred to. A gramme of sodium bicarbonate was introduced in the form of pastilles into the stomach of a large dog; the temperature of the stomach at once rose from 37·5° to 38·3° C., whilst that of the rectum rose from 38° to 38·8° C. This result, which is in complete accord with what I have said about the secretion of gastric juice being stimulated, brings us to the consideration of the INCREASED CHEMICAL DECOMPOSITION AND OXIDATION which occur in the body when the fluids are rendered more strongly alkaline.

In the human subject, the urine can be rendered alkaline by administering, by the mouth, sodium carbonate, or the sodium salts of vegetable acids which are oxidised, in the body, into carbonates. This clearly proves that it is possible to increase the alkalinity of the fluids of our body, though it may be only temporarily. Now, our chemical knowledge teaches us that the decomposition and oxidation of albumen, fat, and other organic substances are promoted by, or even actually depend upon, the solutions being alkaline,—that is to say, we obtain no results in a given time unless this is the case. This also appears to hold good in the living organism, for medical experience in past times has shown that the continuous use of alkaline mineral waters—the amount of food taken remaining the same—

[1] H. Kronecker, 'Verhandl. d. physiol. Ges. Berlin,' 1879, No. 17.

lessens the quantity of fat without causing any disturbance of the general health. A recent series of experiments on men with sodium carbonate and sodium citrate produced the same results.[1]

It has been said[2] that alkaline salts make the bile more dilute, owing to a decrease in all its more important solid constituents. The bile must necessarily also become more alkaline when the alkalinity of the blood is greatly increased. By these means we may possibly reduce the size of gall-stones, promote their passage along the ducts, and check their formation.

The secretion from the RESPIRATORY PASSAGES is also modified by the action of sodium carbonate. This has long been known from the results of clinical experience in the treatment of catarrh of these mucous membranes, and these results have been corroborated by experiments upon animals. Rossbach injected 2 grms. (30 grains) of sodium carbonate, or as much as 1 grm. (15 grains) of ammonium chloride, into the crural vein of an animal whose trachea had been opened.[3] The ammonium chloride, as might have been expected, set up general convulsions, and so interfered with the experiment; the sodium salts produced no effects of that kind. The changes in the mucous membrane of the trachea were, however, of precisely the same nature after both these drugs. They consisted in a blanched or greyish-white appearance of the mucous membrane, with a gradual cessation of the secretion of mucus. Under normal conditions, immediately after removing the secretion from the mucous membrane by means of blotting-paper the mucus was again secreted by the glands, and in two minutes at the most the entire surface was again uniformly covered; but after the injection, at least eight minutes elapsed before there was any sign of even isolated

[1] Stadelmann, 'Verhandl. des 9. Congresses f. innere Med. zu Wien,' 1890, S. 386; Auch, 'Monographie,' Stuttgart, 1890; Görges, 'Arch. für exper. Path. u. Pharmak.,' 1879, Bd. xi, S. 156.

[2] Rutherford, 'Trans. Roy. Soc. Edin.,' 1879, vol. xxix, p. 201; W. Newaschen, 'Zeitschr. f. klin. Med.,' 1884, Bd. vii, S. 609, and Bd. viii, S. 48; the same author and Klikowitsch, 'Arch. f. exper. Path. u. Pharm.,' 1883, Bd. xvii, S. 53.

[3] Rossbach, 'Zeitschrift d. Würzb. Universität,' 1882, S. 36.

drops of mucus, the surface was no longer entirely covered with the secretion, and, if this was again removed with blotting-paper, no mucus made its appearance, the membrane remaining perfectly dry. This effect being uniformly produced by sodium carbonate, we are perhaps justified in asserting that—

Increased alkalinity of the blood diminishes or even completely suppresses the secretion from the mucous membrane of the trachea.

We do not know exactly how this action is brought about; it is not due to the simultaneous blanching of the mucous membrane, for, as we already know, the secretion of mucus continues unchanged when marked anæmia has been artificially caused by stimulation of certain nerves. If this is also the case in human beings, the alkalies must have some special action differing from that which they have generally been supposed to possess. Their action is not to dissolve and liquefy the mucus, thereby facilitating its expectoration, but to directly lessen the hyperæmia and the secretion of mucus resulting from some morbid irritation. The alkalies must therefore be regarded as specific remedies, a view which has certainly often been advanced by those physicians who advocate the use of alkaline mineral waters, such as those of Ems, Neuenahr, Salzbrunn, Fachingen, Carlsbad, Marienbad, Tarasp, Vichy, &c., one chief constituent of which is sodium carbonate. The number of really scientific investigations dealing with the therapeutic aspect of this subject is very insignificant. This may probably be the reason why, in most of the treatises on balneology, the curative effects of the waters are only described in general and vague terms.

The quantity of urine is increased by the use of sodium carbonate or the sodium salts of the vegetable acids. This depends upon a direct stimulation of the secreting renal epithelium.

I have not, so far, drawn any marked distinction between the action of the carbonate and the bicarbonate of sodium, that is between $Na_2CO_3+10H_2O$ and $NaHCO_3$, because it seems very probable that, in the circulation, they both exist in the same condition, that is as a salt in which the quantity of sodium constantly varies. There is a considerable

difference, however, as regards their absorption; the former has a very alkaline reaction, and when given in large doses acts injuriously on the stomach, whilst the latter has a feebly alkaline reaction and is easily tolerated. The carbonate is consequently rarely prescribed internally. In mineral waters it is converted into the milder bicarbonate by the excess of carbonic acid gas.

NATRIUM CARBONICUM SICCUM is a powder obtained by exposing the carbonate to gentle heat, until it has lost four fifths of its water of crystallisation. It is used exclusively in the preparation of powders, because if ordinary sodium carbonate were used, this might be decomposed by the other substances prescribed with it, and the liberated water of crystallisation would render the powder moist.

Much of what has here been said concerning the sodium salts, also holds good for those of POTASSIUM. This metal has however, as I shall have to show later, a very peculiar action, so that the potassium salts differ widely in their effects from those of sodium. The carbonates of both are pharmacodynamically analogous with the sodium or potassium salts of the vegetable acids, among which the acetates may also be included.

If I now heat a neutral or acid salt of one of these vegetable acids in a platinum crucible, and after moistening the ash with water, test its reaction with litmus paper, it is as you see strongly alkaline; on the addition of a little sulphuric acid, an odourless gas is evolved, which renders baryta water turbid. The salt of the vegetable acid has, therefore, been converted, by this process of combustion, into a carbonate.

Wöhler showed that exactly the same process occurs in our bodies.[1] He gave a small dog 3·6 grammes of neutral sodium acetate. The urine which the animal passed at the end of an hour was turbid, very alkaline, and effervesced on the addition of acids. On cooling, phosphates were precipitated. Wöhler himself also took 3·6 grammes (about a drachm) of the same salt, dissolved in water. The urine which was passed at the end of an hour was very acid, but that passed after two hours had elapsed was alkaline and

[1] Wöhler, 'Zeitschr. f. Physiologie,' 1824, Bd. i, S. 143.

effervesced with acids. The urine passed at the end of another hour had the usual amount of acidity. The same results were obtained with doses of from 3·6 to 10·8 grammes (about 1 to 3 drachms) of potassium tartrate and bitartrate, tartarated borax, and tartarated soda. Acid salts were only partially converted into carbonates. After taking cream of tartar, so long as the urine remained alkaline it contained no tartaric acid, but as soon as it acquired an acid reaction, tartaric acid appeared and could be easily precipitated by calcium chloride, and its quantity estimated.

Wöhler also found that after eating a pound of sweet cherries, the urine became as alkaline as if several drachms of some vegetable salt of the alkalies had been taken, and that it had all the usual characteristics of urine produced under such conditions; on the other hand, those fruits which, like currants and lemons, contain an excess of free acids, did not render his urine alkaline.

Much remains to be done in the clinical investigation of the action of these remedies. In the therapeutics of former days, extensive use was made of these organic salts,—in smaller doses, however, than would produce any aperient action,—in order to stimulate the kidneys in cases of enlargement of the liver or spleen, in irritation of the kidneys by uric acid, and in gout itself; they were called "Resolventia." In our own day, they have fallen very much into the background, though the "grape-cure," which is still largely practised, is a remnant of the same line of treatment.

Potassium bitartrate and calcium tartrate are the principal salts contained in good grape juice, and are accordingly to some extent transformed in the system into the corresponding carbonates. In England, potassium tartrate is still used considerably in the above diseases, and this, as we have seen, is justified on chemical and physiological grounds.

We may here also refer to the fatty salt of sodium, which as SAPO MEDICATUS is officinal and which is also employed as ordinary soap for domestic purposes. The medicinal soap is prepared by heating caustic soda with lard and olive oil, whereby the glycerine is set free, and the sodium combining with the oleic, palmitic, and stearic acids forms the soap.[1]

[1] The fats are acid glycerides or acid ethers in which the trivalent

It is white and not rancid, and is soluble in water and alcohol. If we introduced a sufficient quantity of this into the circulation it would appear in the urine as sodium carbonate; we should hardly prescribe it, however, for this purpose, and at present it is simply administered internally as an excipient in the manufacture of pills.

Sulphuric acid also decomposes the fats, the concentrated acid abstracts the water of the fatty molecule, and combines with the glycerine to form sulpho-glyceric acid $C_3H_5.(OH)_2.HSO_4$, which on adding milk of lime is decomposed into calcium sulphate and glycerine.

We now come to a remedy of comparatively recent date, the introduction of which we owe entirely to chemical investigations. I refer to LITHIUM, the officinal form of which is lithium carbonate, Li_2CO_3.

This is a white salt which melts when heated, and solidifies on cooling to a crystalline powder. It forms an alkaline solution with 80 parts of cold water, is insoluble in alcohol, and communicates a carmine colour to the flame of the blowpipe.

molecules C_3H_5 of glycerine are combined with three molecules of a fatty acid. The fats lose three molecules of water and split into the alcohol—glycerine—and the corresponding fatty acids—such as oleic acid $C_{18}H_{34}O_2$ which belongs to the acrylic series—when treated with superheated steam. If sodium or potassium hydrate is now added we obtain glycerine and a soap, whilst if we add hydrate of lead we obtain a plaster, in the chemical sense of the word. The changes may be represented by the following formulæ:

Fat + 3HHO	= glycerine	+ 3	molecules of	acid.
„ + 3NaHO	= „	+ 3	„	soap.
„ + 3Pb(HO)$_2$	= „	+ 3	„	plaster.

Or, more precisely, taking one of the glycerides, viz. trioleïnglyceride, the chief constitent of olive oil, the following represent the changes:

$$C_3H_5.3C_{18}H_{33}O_2 + 3H_2O = C_3H_8O_3 + 3C_{18}H_{34}O_2.$$
$$C_3H_5.3C_{18}H_{33}O_2 + 3NaOH = C_3H_8O_3 + 3NaC_{18}H_{33}O_2.$$
$$2C_3H_5.3C_{18}H_{33}O_2 + 3Pb(OH)_2 = 2C_3H_8O_3 + 3Pb(C_{18}H_{33}O_2)_2.$$

In 1841, A. Lipowitz[1] discovered, whilst investigating the solubility of uric acid, that it has a strong affinity for lithium, and he suggested that this fact might possibly be useful therapeutically. One part of lithium carbonate and one of uric acid are easily dissolved in 90 parts of water at about 50° C. (122° F.), and they remain in solution on cooling; the resulting compound readily dissolves when not dried too completely, in 60 parts of water at 50° C., and on cooling, still remains in solution. Even lithium silicate is decomposed by uric acid, for if lithium mica, lepidolite, which contains 2·5 per cent. of lithium, is finely powdered and boiled with uric acid, the solution after being filtered, and then treated with hydrochloric acid, yields on cooling a precipitate of uric acid. These statements have been confirmed by other observers. L. Binswanger[2] found on experimenting with seven different salts of the alkalies, that lithium carbonate dissolved at least four times as much uric acid as either of the six other salts.

Garrod placed a metacarpal bone, the phalangeal extremity of which was completely infiltrated with gouty deposit, in a small quantity of cold water, to which a few grains of carbonate of lithia had been added. In the course of two or three days, when the head of the bone was examined, no deposit could be seen, and the cartilage appeared to have been restored to its normal state. "In order to demonstrate the superior power possessed by carbonate of lithia over the carbonate of soda or potash in removing the deposits of soda from gouty cartilage," he performed the following experiment:—"Solutions of the salts of lithia, potash, and soda were prepared with one grain of each of the dried salts to the fluid ounce of distilled water; into these were placed small pieces of cartilage completely infiltrated with urate of soda, which were allowed to remain for forty-eight hours. At the end of that time the cartilage taken from the lithia solution was found to have been restored to its natural condition; that from the

[1] A. Lipowitz, 'Annalen d. Chemie u. Pharm.,' 1841, Bd. xxxviii, S. 348.

[2] L. Binswanger, 'Pharmakologische Würdigung der Borsäure und des Borax,' München, 1847, S. 74.

potash was much acted upon, but that which had been submitted to the influence of the carbonate of soda appeared unaltered."[1] Lithium sulphate and lithium chloride act equally efficiently upon sodium urate, and form the comparatively soluble urate of lithium.

Uric acid is also dissolved by lithium chloride to a considerable extent, but is again partly precipitated from this solution on the addition of carbonic acid; in the same way lithium urate is decomposed by prolonged treatment with carbonic acid.[2] This, however, does not occur at 37° C. (98·6° F.), which is the temperature of our blood. We must consequently conclude that the presence of free carbonic acid in the tissues does not prevent the formation of the easily soluble lithium urate.

How far all this may be utilised in the case of human beings who are suffering from a uric acid diathesis, must be determined by clinical investigation. It has been asserted that by the administration of lithium, the removal of uric acid concretions is promoted, the quantity of uric acid in the urine diminished, the deposit of urates prevented, and that simultaneously the gouty condition of the patient is either improved or cured.

Some physicians strongly recommend the use of mineral waters containing lithium, although the quantity present in them is extremely small. The largest amount is contained in the water of the Boniface Spring in Salzschlirf,[3] which contains 0·218 lithium chloride in 1000 parts of water, and the Königs Spring in Elster, which contains 0·108 lithium carbonate in 1000 parts. There are a number of German springs which contain a smaller quantity, among others Assmannshausen on the Rhine, which contains 0·027 of the bicarbonate of lithium in 1000 parts of water. The presence of soda[4] and

[1] A. B. Garrod, 'A Treatise on Gout and Rheumatic Gout,' 3rd edit., pp. 366 and 368, London, 1876. For a criticism of Garrod's views, see Ebstein's 'Natur und Behandlung der Gicht,' Wiesbaden, 1882.

[2] V. Schilling, 'Annalen d. Chemie u. Pharm.,' 1862, Bd. cxxii, S. 241.

[3] Th. Valentiner 'Handbuch d. Balneotherapie,' 1876, S. 268.

[4] E. Pfeiffer, 'Verhandl. d. Congr. f. innere Med.,' 1886, S. 444;

an excess of carbonic acid, together with the naturally warm temperature of the water, may evidently promote the action of lithium and enable the system to tolerate it more readily. With regard to the latter point, I must mention that the lithium carbonate of the Pharmacopœia is not readily tolerated by the stomach, and consequently must only be given in small quantities, such as 0·05 to 0·25 gramme (from three quarters to four grains) in water containing carbonic acid, otherwise it will cause irritability of the stomach, with its usual results. The artificial mineral waters containing lithium have also been recommended.[1]

In a severe case of gout with frequent relapses which came under my care I found the following prescription efficacious, the remedies being easily tolerated in this form:

℞ Lithii Carb., 0·25 (grana iiiss).
Sodii Bicarb., 0·5 (grana viiss).
Pot. Citrat., 1·0 (grana xv).
M. ft. pulv. D. tal. dos. No. 20.
Sig.—One powder to be taken night and morning in seltzer water.

In another case very good results followed the daily use of 1 gramme (15 grains) of lithium carbonate dissolved in half a litre (about a pint) of seltzer water.

The following statement[2] has been published with regard to the action of the alkaline salts on the excretion of uric acid:—"The water from the springs of Fachingen on the Lahn contains in 1000 parts 3·65 parts of sodium bicarbonate, 0·007 of lithium bicarbonate, and 0·57 parts of magnesium bicarbonate. The continuous use of this water promotes the elimination of uric acid from the system, prevents the formation of free uric acid in the urine, and lessens the gouty deposits in the joints." I have found by experiments upon myself that Fachingen water renders the urine slightly alkaline. This result is essentially due to the sodium car-

K. Frickhinger, Doctordissertation, München, 1887; L. Fürst, 'Deutsche med. Zeitung.,' 1890, No. 79.

[1] Leichtenstern, 'Allgem. Balneotherapie,' 1880, Bd. ii, Th. 1, S. 380. (In v. Ziemssen's 'Allgem. Therapie.')

[2] E. Pfeiffer, loc. cit., 1888, S. 327; C. Posner, 'Berl. klin. Wochenschrift,' 1890, No. 27.

bonate, and not, of course, to the trifling quantity of lithium carbonate which the water contains.

Instead of the carbonate, many physicians prescribe lithium salicylate, LITHIUM SALICYLICUM $Li.C_7H_5O_3$, which is now officinal in Germany. It is a white, crystalline, odourless powder with a sweetish taste, dissolving readily in water and in alcohol.

It may be prescribed in larger doses than the carbonate, being more readily tolerated by the stomach. From 0·5 to 1·0 gramme (7½ to 15 grains) may be administered several times a day. It has been proved that salicylic acid increases the excretion of uric acid by the kidneys, and in cases of acute articular rheumatism is said to give better results sometimes than sodium salicylate.

According to E. Pfeiffer, NATRIUM PHOSPHORICUM, Sodii phosphas, phosphate of soda, or disodic phosphate, acts in a similar manner. It consists of colourless, transparent crystals, which are efflorescent and taste like common salt. It is soluble in six parts of water, the solution having a faintly alkaline reaction, and it has the following composition:

$$Na_2HPO_4 + 12H_2O.$$

It is a constituent of normal human blood, and therein can combine with or give off carbonic acid gas, according as it is influenced by tension, temperature, or by the presence of other acids—

$$Na_2HPO_4 + CO_2 + H_2O = NaH_2PO_4 + NaHCO_3.$$

That is to say, it is transformed into monosodic phosphate and sodium bicarbonate, which at any moment may be reconverted into the original compound. The dose of disodic phosphate must be regulated according to its toleration by the stomach and intestines. When given in large single doses of 15 grammes (about 4 drachms) it causes diarrhœa, an effect which must of course be avoided whenever our object is to introduce the salt into the blood.

The carbonates and hydrates of calcium and magnesium act similarly to lithium carbonate on the system.

CALCIUM CARBONICUM PRÆCIPITATUM, $CaCO_3$, is a white micro-crystalline powder, almost insoluble in water, and is

precipitated by mixing together a solution of carbonate of sodium with one of calcium chloride.

It is prescribed in cases associated with morbid acidity of the stomach as well as in cases of chronic diarrhœa, and its use is undoubtedly often beneficial. This is explained by the fact that the finely divided calcium carbonate forms a dense compound with fatty substances which is not easily absorbed, and which serves as a protective covering for abraded places in the intestines. It further combines in the intestines[1] with any irritating acids formed there from the fermentation of carbohydrates which may have been taken in excess.

It has also been asserted that carbonate of lime influences the quantity of urine and the excretion of phosphoric acid. A tolerably large number of investigations have been made on this subject, but no definite results have been arrived at. Lehmann[2] maintains that the administration of 5·0 grammes (75 grains) of calcium carbonate or of magnesium carbonate increases the quantity of urine in healthy individuals. Smaller quantities of magnesia, such as 2·0 grammes (30 grains), as well as a mixture of the two carbonates above mentioned, given in the proportion in which they occur in one litre of Wildungen water, have the same effect. The diuretic properties of the Wildungen water depend not only on the carbonic acid but also on the two carbonates of the alkaline earths which it contains. After the administration of these salts, or of Wildungen water, the urine ceases to deposit urates, even though it may previously have done so for a considerable period. If the carbonates of lime or magnesia are swallowed without being first dissolved, they pass into the urine in considerable quantity; they do not, however, render it neutral or alkaline.

The medicinal waters containing calcium carbonate which are most frequently employed are those of Lippspringe, Wildungen, Inselbad near Paderborn, and Baden near Zürich. Most chalybeate waters also not infrequently contain a considerable amount of calcium carbonate, and together with it sometimes calcium sulphate.

[1] J. Munk, 'Arch. f. path. Anat.,' 1882, Bd. xcv, S. 419.

[2] E. Lehmann, 'Berl. klin. Wochenschr.,' 1882, No. 21.

Physiological investigations have shown us that compounds of lime and magnesia, especially their phosphates, are present in all organised bodies and are even essential to life. On the other hand, it is noteworthy that if the chloride of either of these alkaline earths be directly injected into the blood, in the same dose which in the case of sodium chloride would be perfectly innocuous, it first stimulates and then paralyses the action of the heart, and subsequently induces paralysis of the nervous centres.

The metals of the different alkaline earths may, as regards their poisonous activity, be arranged in descending intensity as follows: barium, potassium, magnesium, calcium, strontium, sodium.[1]

By strongly heating calcium carbonate and charcoal together, CO and CO_2 are evolved and we obtain calcium oxide, CaO, which on the addition of water is converted into calcium hydrate, $Ca(OH)_2$. One part of this dissolved in 100 parts of water forms the officinal AQUA CALCARIÆ, LIQUOR CALCIS, or lime-water, a clear, colourless, strongly alkaline liquid, which on exposure to the air absorbs carbonic acid, and calcium carbonate is again formed. Lime-water is employed as an addition, in the proportion of about 1 part to 20 of milk, in order to impede the coagulation of the latter in the stomachs of children and delicate people, and to render the curd less dense; secondly, to check diarrhœa, especially if dependent upon ulceration of the intestines, when it acts in the same way as the carbonate. It is also applied locally, or used as an inhalation to liquify croupy or diphtheritic exudations, which are easily decomposed by it, the lime-water dissolving[2] the mucin in which the fibrin is lodged. The lime-water also acts as an astringent upon the mucous membrane of the part, as it does upon mucous membranes in general. Mixed with an equal part of linseed oil, it is applied as a soothing liniment to burns.

MAGNESIUM CARBONICUM, MAGNESIA CARBONAS, carbonate of magnesia, magnesia alba, has the following formula:

$$3MgCO_3 + Mg(HO)_2 + 4H_2O.$$

[1] C. Mickwitz, 'Vergleich. Unters. über d. physiol. Wirk. d. Salze der Alkalien und alkal. Erden,' Doctordiss., Dorpat, 1874.

[2] Harnack, 'Berl. klin. Wochenschr.,' 1888, S. 352.

It is a very light, flocculent powder, almost insoluble in water, but imparting to it a feeble alkaline reaction. It is much employed as an "absorbent" in cases of morbid acidity of the stomach; the greater part of it passes undissolved through the intestines, a small portion is dissolved by the acid secretions, and is absorbed and passes into the circulation. I have already stated all that is known of the physiological action of magnesium carbonate when discussing that of calcium carbonate. If frequently administered it may, in combination with the fæces in the large intestine, lead to the formation of large masses, consisting of ammonio-magnesium phosphate, and give rise to considerable disturbance of the system. Being so light and flocculent, it is best when giving it to shake it up with water. The dose is from 0·1 to 0·5 gramme ($1\frac{1}{2}$ to $7\frac{1}{2}$ grains). In large doses it acts as a purgative. By ignition the carbonic acid and water are expelled, and MgO remains behind as MAGNESIA USTA, calcined magnesia, or light magnesia. It is a very light, fine and white powder, with a weak alkaline reaction, and is very slightly soluble in water. Calcined magnesia absorbs carbonic acid in a remarkable manner, and in the stomach and intestinal canal is thereby converted into magnesium bicarbonate. One gramme (15 grains) of a thoroughly calcined specimen will absorb 1091 c.cm. (about 75 cubic inches) of carbonic acid gas, and consequently magnesia may sometimes be useful in lessening flatulent distension of the intestine. Complete relief, however, cannot be attained by this chemical action, owing to the presence of other gases besides carbonic acid, which are not absorbed by the magnesia. It is often useful as a laxative. In cases of poisoning by corrosive acids, the use of magnesia is preferable to that of its carbonate, since carbonic acid is liberated from the latter, causing distension of the stomach and intestines, as well as the formation of emboli in the eroded vessels. Magnesia, when administered in excess, produces with corrosive metallic salts in the stomach a precipitate of the metal which is only very slightly soluble. With arsenious acid it forms a compound which is almost insoluble in the alimentary canal.

The dose of calcined magnesia is from 0·1 to 0·5 gramme

($1\frac{1}{2}$ to $7\frac{1}{2}$ grains). To act upon the bowels, the larger dose must be repeated two or three times or oftener. It is best given either as a powder, or suspended in water, $7\frac{1}{2}$ grains being taken every two hours.

In the POTASSIUM COMPOUNDS of the Pharmacopœia the potassium is here altogether of secondary importance. The medicinal action of potassium permanganate depends essentially upon the oxygen, of potassium iodide upon the iodine, of potassium bromide upon the bromine, of potassium chlorate upon the chloric acid, &c. In a general way, it is either on account of the finer crystallisation, or the greater stability of the potassium salts, or even fortuitous custom, that a preference arises for them pharmacologically. So far as the alkaline nature of these salts is concerned,—and it is for this reason they are included in the group of remedies we are at present considering,—we find that the two carbonates of potassium are of less service, and are less frequently employed than the corresponding salts of sodium, owing to the milder, that is to say, the less caustic or irritant action of the latter.

The potassium salts, especially the officinal ACETATE, are supposed to possess a more marked DIURETIC action than the corresponding salts of sodium. This depends upon the direct stimulating effect which they have on the secreting epithelium of the kidneys. The difference, moreover, between the action of potassium and sodium nitrate is very distinct, the former possessing poisonous properties, the latter producing little or no effect on man.

On a previous occasion, when discussing the actions of potassium iodide and potassium bromide, I pointed out that when these salts are taken for some time, or when only two or three doses are taken by persons who are readily influenced by them, the heart becomes unpleasantly affected. The pulse is reduced in frequency, becomes weak and irregular, whereas sodium iodide and sodium bromide have no such action. It is only within recent years that attention has been called to the great difference in the action of these two metals on the heart.[1]

[1] L. Grandeau und Cl. Bernard, "L'action comparative des sels de potassium, de sodium et de rubidium, injectés dans les veines," 'Journ.

I inject under the skin of a rabbit weighing about 800 grammes, 3·5 grammes of potassium chloride dissolved in 10·0 grammes of lukewarm water. In fifteen minutes the animal lies with its forelegs and head resting on the table. When pushed it tries to move, but it is now evident that the hinder limbs are distinctly paralysed. The respiration remains at the normal rate. In about eight minutes more the heart's impulse is weak, its frequency diminished, and in about five minutes more the beat can no longer be felt. The animal becomes cyanosed, and dies after a few distinct convulsive movements. The heart, on being exposed, makes only a few faint contractions, and if irritated with a needle reacts very slightly.

The cause of death is still more distinctly demonstrated, if into a stronger animal I inject through the jugular vein direct into the heart 0·1 gramme (1½ grains) of sodium chloride in 1·0 gramme (15 grains) of lukewarm water and register the beats by passing a needle, with a small feather at the end, into the heart and noting its movements. Not the slightest reaction takes place. I repeat the experiment, now with 0·1 gramme of potassium chloride, a chemically neutral salt, and apparently harmless like common salt. Immediately on the introduction of the potassium chloride the movements of the needle become irregular, slight, and infrequent; the animal is convulsed, apparently as the result of the sudden disturbance of the circulation, the movements of the heart cease entirely, and the animal dies. If the heart is immediately exposed it presents much the same conditions as above described.

This specific poisonous action of potash on the heart has, since 1864, been investigated by numerous observers who have not arrived at any very distinct conclusion as to its cause. It has been suggested as an explanation that as the blood serum contains very little potash, whereas the blood-corpuscles contain a good deal, this foreign ingredient in the serum acts prejudicially. Further, it is maintained that the contractile substance of the heart is a molecular

de l'anat. et de la physiol.,' 1864, vol. i, p. 378; E. Kemmerich, 'Arch. f. d. ges. Physiol.,' 1868, Bd. i, S. 120, und 1869, Bd. ii, S. 49; G. Bunge, ibid., 1871, Bd. iv, S. 235.

combination of albumen with potassium salts, and that any large addition of potassium salts would modify this combination. Both these explanations fail, since according to the statements of Grandeau, the salts of rubidium—an element which is quite foreign to the system, but chemically closely allied to potash—produce no poisonous effects when injected in the same manner.[1] In the first experiment we noticed that when the potash salt was injected under the skin motor paralysis of the limbs took place even before the heart was paralysed; also that the nerve centres were affected by the excess of potash present in the circulation. The question now arises, how is it that when taking a considerable amount of potash salts in our food no poisonous effects are produced? Potatoes, for instance, have been found, as the mean result of ninety analyses, to contain, in their natural condition, about 1 per cent. of ash, of which about 60 per cent. is potash.[2] If, therefore, a person eats 1 kilo (about 2¼ lbs.) of potatoes he takes about 6 grammes (90 grains) of potash, which corresponds to 18·5 grammes (4·8 drachms) of potassium phosphate. In addition, meat and other kinds of food are eaten which also contain considerable quantities of this salt.

That such an amount of the potassium salts should not produce poisonous effects when introduced into the alimentary canal is due to its being slowly absorbed and rapidly excreted from the system.

[1] J. Blake, 'Centralb. f. d. med. Wissensch.,' 1886, S. 97.

[2] According to J. König, 'Chemie der menschl. Nahrungs- und Genussmittel,' 1883, S. 429.

XVIII.

Iron—Its use in chlorosis—Discussion as to its value and mode of action—Officinal preparations—Hypodermic administration of the remedy—Its poisonous effects—Phosphorus—Its introduction and use as a remedy—Experiments on animals—Administration in osteomalacia and rickets—Calcium phosphate as a therapeutic agent—Poisonous effects of phosphorus—Explanation of its action.

In determining the value of iron as a remedial agent we have two facts to guide us; the one physiological, the other therapeutical. The first is that iron is an essential constituent of hæmoglobin, a substance which plays an important part in the animal system; the other fact is that we are able to cure the morbid conditions associated with chlorosis by the proper administration of this remedy.

This effect is most clearly shown in the typical chlorosis of young women, in whom, as a result of the diminished quantity of red blood-corpuscles, the activity both of the mental and bodily functions is lessened. Depressed spirits, disinclination for work, enjoyment, or exertion of any kind, feebleness of the muscles of the heart and of the respiration, failure of appetite, disorder of the digestive function, diminution of the various secretions, headache, giddiness, disturbed or complete loss of sleep, suppressed or diminished catamenial discharge, a pallid or greenish complexion (hence the term "green-sickness" sometimes used in England) are among the general symptoms associated with this disorder, which sometimes, notwithstanding the most nutritious and suitable diet, change of residence, and mental rest, proves very intractable. The condition of the patient, however, begins to improve directly we have recourse to the adminis-

tration of iron in some suitable form and under proper precautions. The functional activity of every organ is stimulated, and tissue metamorphosis, the action of the heart, the breathing, the temperature, and the desire for food, &c., return to their normal conditions. The recovery from a morbid to a healthy condition of the system results from an increased formation of red blood-corpuscles.

The internal use of iron, as a remedial agent, dates back to ancient times. I pass over the fantastic reports of its curative effects published by the followers of Hippocrates and of Dioscorides, and those, of a much later date, of Saint Hildegarde. The alchemists of the sixteenth century, who concerned themselves chiefly with the metals, brought it prominently into use. Paracelsus greatly extols, after his usual fashion, the action of colcothar (peroxide of iron) in combination with common salt and myrrh in cases of dropsy. I can enumerate no fewer than forty-five separate monographs on iron published between the year 1580 and the end of last century, besides numerous others which appeared in various publications during the latter part of that period.

Within the last few years considerable discussion has taken place, and many experimental investigations have been made with regard to the curative effects of iron when administered in cases of chlorosis, but as yet no very clear or definite conclusion has been arrived at on the subject. The following, however, are the chief facts which have been determined.

The body of a healthy adult contains about 3 grammes (46 grains) of iron, the greater part of which is contained in the hæmoglobin.

The iron ordinarily contained in the food is absorbed by the lining membrane of the alimentary canal, and passes into the circulation. This lining membrane also excretes by far the largest portion of iron from the system. Iron is also eliminated in the urine, but in so minute a quantity—in adults amounting only to a few milligrammes daily—that, so far as tissue change is concerned, this may be neglected.

The food taken by a chlorotic individual generally contains sufficient iron to replace the loss of that excreted by the bowels. Other causes, therefore, than an insufficient supply

must exist, which interfere with or prevent a normal amount of hæmoglobin being elaborated from the iron. No satisfactory explanation, however, has hitherto been advanced as to the nature of these causes.

From the results of experiments on animals it has been maintained that iron, when artificially added to the usual food, is NOT absorbed by the healthy intestine, but passes off with the fæces. These experiments, however, are by no means conclusive, since the quantity of iron concerned in the daily tissue change of the system is so small as to be within the limits of experimental error in any chemical analysis.

Moreover the liver possesses the power of abstracting iron from the blood and retaining it. The iron is gradually restored to the blood, to be taken up by the epithelium of the lining membrane of the alimentary canal, and slowly excreted into the canal.

By applying ammonium sulphide to the tissues, and observing the chemical reaction under the microscope, it can be shown that there are certain cells in the spleen, in the marrow of the bones, and in the lymphatic glands, which are largely impregnated with iron, and that in the liver also it is deposited in the hepatic cells. The tissues above mentioned evidently attract iron more strongly than do other parts of the animal body. If then a certain quantity of iron is added to the ordinary food, the amount in the whole system, and more especially in the liver, is distinctly augmented. We must, therefore, conclude that some of the additional iron has been absorbed by the alimentary canal, and, passing into the circulation, has been brought into contact with the tissue cells. In chlorosis there is diminished blood-formation, and the only conclusion we can arrive at is that the organs fail to discharge their function, the power of development of the blood-forming tissues, such as the marrow, &c., is lowered, the result being that they cease to utilise the ferruginous nucleo-albumin contained in the blood which circulates through them, much in the same way as the cartilages in rickety subjects fail to absorb the calcareous salts, or as muscles which are wasting fail to utilise the albuminous elements, although these substances are abun-

dantly present in the blood which is brought in contact with the tissues. We may summarise the whole matter as follows :—

It is probable (1) that the functional activity of the blood-forming organs, which is lowered or suppressed in chlorosis, requires a stimulus or impulse; (2) that iron, when carried in the circulation to these organs in increased quantity, acts as a chemical stimulus, and not being an entirely foreign constituent is less injurious in its action than other stimulants. This view appears all the more plausible as other substances when administered act in the same way as iron. I need only refer to the action of manganese, arsenic, phosphorus, and mercury.[1] Chlorosis can be

[1] V. Ranieri, "Der therapeutische Wert des Quecksilbers in der Behandlung der Anämie," 'Therap. Wochenschr.,' Wien, 1895, Nos. 19 u. 20 (Medic. Klinik in Pisa). The following reports of various experimental investigations regarding the conditions in which iron exists in the organism may be referred to with advantage:—H. V. Hösslin, "Ernährungsstörungen infolge Eisenmangels in der Nahrung," 'Zeitschr. f. Biologie,' 1882, Bd. xviii, S. 612; H. Quincke, 'Arch. f. Anat. und Physiol.,' 1886, S. 757; A. Meyer, 'De ratione qua Ferrum mutetor in corpore,' Diss., Dorpat, 1850; M. J. Dietl und C. Heidler, 'Vierteljahrschr. für prakt. Heilkunde,' 1874, Bd. cxxii, S. 89; H. Nasse, "Die Wirkung des der Nahrung zugesetzten Eisens auf das Blut," 'Sitzungsb. d. Ges. z. Beförd. d. ges. Naturw.,' 1877, No. 3. Ref. 'Centralblatt f. med. Wiss.,' 1877, S. 646; E. W. Hamburger, "Die Aufnahme und Ausscheidung des Eisens," 'Zeitschr. f. physiologische Chemie,' 1878, Bd. ii, S. 191; R. Gottlieb, 'Arch. f. exper. Path. u. Pharmak.,' 1889, Bd. xxvi, S. 139; Kölliker u. Müller, "Einige Untersuchungen über die Resorption von Eisensalzen," 'Verhandl. der phys.-med. Ges. Würzburg,' 1855, Bd. vi, S. 515; G. Lewald, 'Untersuchungen über den Uebergang von Arzneimitteln in die Milch.,' Breslau, 1857, S. 2 (Habilitations-Schrift); Bistrow, "Der Uebergang des Eisens in die Milch bei Tieren," 'Arch. f. pathol. Anat.,' 1868, Bd. xlv, S. 98; J. Dietl, 'Sitzungsber. d. k. k. Akad.,' Wien, 1875, Bd. lxxi, ii, S. 420; A. Kunkel, 'Arch. f. ges. Physiol.,' 1877, Bd. xiv, S. 353, 1891, Bd. l, S. 1; E. Hamburger, a. a. O., 1880, Bd. iv, S. 248; C. A. Socin, 'Zeitschr. f. physiol. Chemie,' 1891, Bd. xv, S. 93; Kobert, 'Arch. f. exper. Pathol. u. Pharmak.,' 1883, Bd. xvi, S. 380; G. Bunge, 'Zeitschr. f. physiol. Chemie,' 1889, Bd. xiii, S. 399; 'Lehrb. d. physiol. u. pathol. Chemie, 1894; Gottlieb, 'Zeitschr. f. physiol. Chemie,' 1891, Bd. xv, S. 317; C. Jacobi, 'Arch. f. exper. Path. und Pharmak.,' 1891, Bd. xxiii, S. 256; R. Stockman, "The Treatment of Chlorosis by

treated successfully with these remedies also, notwithstanding the fact that they are certainly not constituents of hæmoglobin.

We will now discuss the various officinal PREPARATIONS OF IRON, and in dealing with each one I will point out what advantage or disadvantage it may possess, and what are the special indications for its use. The first preparation is metallic iron in the form of—

FERRUM PULVERATUM, limatura martis præparata, powdered iron. This is a fine, heavy powder, with a somewhat metallic lustre. If the metal is contaminated with sulphur it may give rise to disagreeable eructations, owing to the formation of sulphuretted hydrogen in the stomach. In order to obviate this, and at the same time to administer the remedy in a more minute state of subdivision, and one which is more easily tolerated by the stomach, we use FERRUM REDACTUM, reduced iron. This is prepared by passing dry hydrogen over pure ferric oxide at a red heat, whereby the oxide is reduced to the metallic state, $Fe_2O_3 + 3H_2 = 3H_2O + 2Fe$. It is a fine greyish-black, lustreless powder, and usually contains a variable amount of magnetic oxide of iron, Fe_3O_4.

These two preparations of iron may be given either in the form of pill or powder, in doses of from 0·02 to 0.1 gramme (from $\frac{1}{3}$ to $1\frac{1}{2}$ grains). Opinions differ widely as to any advantage which either of these forms of iron possess over the various soluble preparations. Leube[1] recommends the following prescription :—Ferr. redact. 5·0 (grana 75), Pulv. rad. Alth. 4·0 (grana 60), Gelatin. q.s. ut ft. pilul. No. 90, D. S., one pill, gradually increasing the dose to three, to be taken three times a day. When carefully prepared, these pills are quite soft, and on this account are easily tolerated by delicate stomachs.

We will now consider those preparations of iron which are chiefly employed internally, and will arrange them in three groups; first, those containing ferrous oxide, FeO,

Iron and some other Drugs," 'Brit. Med. Journ.,' 1893, May 6th; C. von Noorden, "Altes und Neues über Pathologie und Therapie der Chlorose," 'Berl. klin. Wochenschr.,' 1895, No. 9.

[1] Leube, 'Zeitschr. f. klin. Med.,' 1883, Bd. vi, S. 204.

the hydrate of which is first white and then greenish; secondly, those containing black magnetic oxide, Fe_3O_4; and lastly, those containing the reddish-brown ferric oxide, Fe_2O_3.

FERRUM CARBONICUM SACCHARATUM, saccharated carbonate of iron, is prepared by precipitating ferrous sulphate with sodium bicarbonate, $FeSO_4 + NaHCO_3 = FeCO_3 + NaHSO_4$, and then adding powdered sugar of milk, or cane-sugar. It is a greenish-grey powder, with a sweet, very feebly chalybeate taste, and contains 10 per cent. of iron. When treated with hydrochloric acid it dissolves, with free evolution of carbonic acid gas, and forms a greenish-yellow fluid. If it only effervesces slightly on the addition of the acid, or if it has a brown colour, it should be rejected, for it has been more or less converted into ferric oxide, the salts of which are less easily tolerated by the stomach than those of ferrous oxide. Ferrous carbonate readily undergoes decomposition if exposed to the air, giving off carbonic acid and absorbing oxygen; by enveloping the carbonate in sugar this change is retarded. The dose is from 0·2 to 2 grammes (from 3 to 30 grains). PILULÆ FERRI CARBONICI, iron pills, are prepared by mixing freshly precipitated carbonate of iron with powdered sugar, powdered marsh-mallow root, and honey. Each pill contains 0·02 gramme ($\frac{1}{3}$ of a grain) of iron.[1]

FERRUM LACTICUM, lactate of iron, $Fe(C_3H_5O_3)_2 + 3H_2O$, is in the form of greenish-white crystalline crusts, or of a crystalline powder, with a peculiar but not very distinctive taste. It dissolves slowly in forty parts of water, the solution having a slightly acid reaction. It is insoluble in alcohol, and may be given, in the form of powder or pill, in doses of 0·02 to 0·2 gramme (from $\frac{1}{3}$ to 3 grains).

LIQUOR FERRI IODATI is a solution of iodide of iron, FeI_2, in water. It has a greenish colour, and should only be used in the recently prepared state. It contains 50 per cent. of iodide of iron. As the iodine is also an active agent in this compound, it is a useful remedy in the scrofulous diseases of childhood, and in general is easily tolerated. The iodide is readily decomposed, the iron being converted into ferric oxide, and free iodine being liberated, so that when the

[1] Pilula Ferri Carbonatis, 'Ph. Brit.,' contains four parts of saccharated carbonate of iron and one part of confection of roses (Transl.).

solution is given in large doses it may act as an irritant. When given in small doses, the free iodine is absorbed from the alimentary canal, and the use of the remedy is often of service in glandular enlargement and similar conditions, either in the abdomen or elsewhere.

As the iodide of iron is much less liable to undergo decomposition when a considerable quantity of sugar has been added to the aqueous solution, the SYRUPUS FERRI IODATI is a form which is very generally employed; 100 parts of the syrup contain 5 parts of iodide of iron, and consequently 0·9 of iron and 4·1 parts of iodine. It is colourless when freshly prepared, and afterwards becomes yellow; after exposure for some time to the air the iodine is liberated, the iron is oxidised, the colour becomes reddish brown, and the preparation is no longer fit for use. (Light retards this decomposition, because the reduction of the salts of ferric oxide is promoted by the action of direct light, and consequently the oxidation of the salts of ferrous oxide is impeded.) The syrup is more particularly employed in the disorders of childhood, the dose being from ten to twenty drops. It must be borne in mind that this syrup cannot be used, as some others are, to cover the flavour of nauseous drugs.

FERRUM SULPHURICUM, Ferri Sulphas, sulphate of iron ($FeSO_4 + 7H_2O$). Of this there are three officinal varieties. The really pure salt consists of small granular crystals efflorescing in dry air, forming with two parts of water a solution, the reaction of which is almost neutral to test-paper. If 100 parts are exposed to a temperature of 100° C. (212° F.) until they lose from 35 to 36 parts in weight, we obtain FERRUM SULPHURICUM SICCUM, Ferri Sulphas Exsiccata, dried sulphate of iron, a fine white powder, which dissolves slowly in water. Both these preparations are used internally, the latter either in solution or made into pills or powders. Large doses of sulphate of iron are inadvisable, as the stomach does not readily tolerate them, and they may cause erosion of the gastric mucous membrane. If a solution of this salt is exposed to the air for some time it becomes cloudy and yellowish, from the formation and precipitation of peroxide and hydrated peroxide. The dose of the crystalline ferrous sulphate is from 0·05 to 0·1 gramme (¾ to 1½

grains); of the dried from 0·03 to 0·05 gramme (from about ½ to ¾ of a grain). They are, however, not much employed internally.

The preparations of iron just referred to have, when recently prepared, a greenish colour, and give with potassium ferricyanide, $K_6Fe_2Cy_{12}$, a deep blue precipitate, and with potassium ferrocyanide a bluish-white precipitate. The following preparation, however, has a black colour, and gives a blue precipitate with both these reagents, thereby demonstrating the presence in it of magnetic oxide of iron, Fe_3O_4.

EXTRACTUM FERRI POMATUM. This is prepared by boiling iron filings with the juice of unripe apples, diluting the decoction with water, filtering and then evaporating the filtrate to a suitable consistence. It has a dark green colour, and contains from 5 to 8 per cent. of iron. The dose is from 0·1 to 0·5 gramme (1½ to 7½ grains) and may be given as a pill. A solution of one part of the extract in nine of Aqua Cinnamomi Spirituosa forms the TINCTURA FERRI POMATA, tincture of malate of iron, which may be prescribed in doses of from 10 to 30 minims. It is a dark brown fluid having the odour of cinnamon and a slight ferruginous taste, and is miscible in all proportions with water without becoming turbid.

Iron in combination with the vegetable acids—malic, citric, and tartaric acids—is NOT PRECIPITATED by the alkalies, and consequently remains in solution after passing into the small intestines. The compounds of ferrous oxide with the vegetable acids do not form precipitates with albumen so readily as is the case with other compounds of iron, and consequently produce less irritation in the alimentary canal.

We now come to the preparations containing ferric oxide, and will consider in the first place, three preparations of the oxide itself.

FERRUM OXIDATUM SACCHARATUM, saccharated ferric oxide. This is prepared by mixing the precipitate of ferric oxide, obtained by adding sodium carbonate to a solution of perchloride of iron, with cane-sugar; it is a reddish-brown powder, with a slight chalybeate taste; 100 parts contain 3 of iron, and one part added to 20 parts of hot water forms a clear reddish-brown solution, having a very faint alkaline

reaction. It is said to be readily assimilated, and in any case is pleasant to the taste, and on this account is largely employed as a remedy for children. It is administered exclusively as a powder in doses of 0·2 to 1 gramme (3 to 15 grains) two or three times a day. In cases of poisoning by arsenic, when there is reason to believe that the poison is still in the stomach, doses of 10 grammes (150 grains) may be administered. To this, however, I shall refer again later on.

Syrupus Ferri Oxidati. A mixture of equal parts of saccharated ferric oxide, water, and simple syrup. It has a dark reddish-brown colour; 100 parts of the syrup contain one part of iron. From half a teaspoonful to a teaspoonful is the dose for a child.

Neither of these preparations of ferric oxide should be mixed with water, otherwise the ferric oxide, which in the syrup is merely in a state of suspension, and not dissolved, will settle to the bottom of the vessel.

Liquor Ferri Oxychlorati, solution of ferric oxychloride, a reddish-brown, clear, odourless liquid, with a neutral reaction and very slight astringent taste, which contains about 3·5 per cent. of iron. This is a simplified form of Ferrum Dialysatum, a remedy which has been in general use for a considerable period, and which used to be prepared by placing an aqueous solution of ferric chloride in a covered dialyser. The hydrochloric acid in this was disengaged and diffused through the dialyser in larger quantity[1] than its equivalent of ferric oxide, and ferric oxide dissolved in ferric chloride remains on the dialyser. The process in its simplest form may be thus represented.

$$2Fe_2Cl_6 + 3H_2O = 6HCl + Fe_2O_3 + Fe_2Cl_6.$$

This process has been superseded by another in the Pharmacopœia, which directs that the freshly precipitated ferric hydrate, after being washed and the superfluous moisture expressed, should at once be dissolved in just sufficient hydrochloric acid to form a solution of neutral oxychloride, that is a solution of ferric hydrate in ferric chloride. Many practitioners report favourably, as was formerly the case with

[1] A. Kossel, "Die chemischen Wirkungen der Difusion," 'Zeitschr. f. physiol. Chemie,' 1878, Bd. ii, S. 158.

Ferrum Dialysatum, of this officinal solution, and state that it is readily tolerated by the system. The dose is from 10 to 40 minims.

The following is perhaps better adapted for use when the digestive organs are very sensitive, and is the form in which iron is, generally, most easily assimilated.

Liquor Ferri Albuminati, solution of albuminate of iron. This is prepared by mixing the previous solution with the officinal dried egg-albumen and water, dissolving the resulting precipitate in solution of soda, and then adding alcohol, cinnamon water, and aromatic tincture. This solution is clear by direct light, but appears slightly turbid by reflected light, is of a reddish-brown colour, and has a very slightly alkaline reaction. It has a faint taste of cinnamon, but that of iron is hardly perceptible; 1000 parts contain about four of iron. It may be given in doses of a teaspoonful without any admixture.

The albumen ovi siccum above mentioned is either in the form of transparent horny masses similar in appearance to gum arabic, or of a yellow, odourless, and tasteless powder. It is soluble in water, and forms a neutral turbid solution.

The two following are ferric salts :

Liquor Ferri Acetici, solution of acetate of iron. A reddish-brown fluid with a feeble odour of acetic acid, which deposits when heated, a reddish-brown precipitate. It contains about 5 per cent. of iron, and is prescribed in doses of 10 to 30 minims. When mixed with alcohol and acetic ether, it forms

Tinctura Ferri Acetici Ætherea, ethereal tincture of acetate of iron. A clear, dark, brownish-red fluid, which is only transparent in thin layers. It smells of acetic ether, has an acid, astringent, and rough taste, and mixes in all proportions with water, forming a clear solution. It contains about 4 per cent. of iron, and is given in doses of from 10 to 30 minims.

The following are sometimes given internally, but are more frequently used externally:

Liquor Ferri Sesquichlorati, solution of perchloride of iron. A clear orange-brown solution which contains 10 per cent. of iron. It is prepared by dissolving iron wire in

hydrochloric acid, then adding nitric acid and heating the solution until it ceases to give a blue coloration on the addition of potassium ferricyanide, showing that ferrous chloride is no longer present.

The solution of the perchloride of iron is applied locally as an astringent in cases of hæmorrhage, either diluted with from 50 to 500 parts of water, or the undiluted solution may be poured upon charpie, which should be squeezed as dry as possible, and then applied to the bleeding part. It checks the hæmorrhage by exciting contraction of the muscular coat of the bleeding vessels, and not by coagulating the blood and forming clots at their orifices (Rossbach). Owing to its caustic properties, which are due to the rapid evolution of chlorine, it must be employed with great caution, especially when administered subcutaneously, in a dilute form (1 in 300). When given internally in doses of five to ten drops in water, it is doubtful whether it has any effect upon hæmorrhage from distant organs, but it is recommended, by competent observers, in hæmorrhage from the intestinal canal itself, such as occurs in typhoid fever and gastric ulcer, and in these cases may be of service owing to its constringing effect upon the blood-vessels. Where this cannot be effected by direct action on the part, it is supposed to result from reflex irritation of the stomach.

Ferrum Sesquichloratum, perchloride of iron, $Fe_2Cl_6 + 12(H_2O)$, is a yellow, crystalline, dry mass which readily deliquesces in damp air, melts at a gentle heat, and is soluble in alcohol and water. It is prepared by evaporating, on a water or steam bath, 1000 parts of the solution of the perchloride of iron down to 483 parts; the residue is then placed in a covered vessel in a cool dry place until it has completely solidified.

The perchloride of iron must be regarded more as a preparation of chlorine than as a preparation of iron, since it readily parts with some of its chlorine. To demonstrate this, I need only add to a solution of potassium iodide, mixed with a little mucilage of starch, a drop of the diluted officinal Liquor Ferri Sesquichlorati. It immediately produces a deep blue colour, owing to the evolution of iodine precisely as if I had added pure chlorine water—$2KI + Cl_2$

$= 2KCl + I_2$. Tincture of guaiacum, the well-known test for nascent oxygen, also acquires a blue colour on the addition of a drop of the liquor. This reaction depends upon the fact that an unsaturated atom of oxygen is liberated, and then combines with any oxidisable body. This reaction in its simplest form may be expresed by the following equation:

$$H_2O + Cl_2 = 2HCl + O.$$

Two preparations for internal administration are obtained from the preceding;

TINCTURA FERRI CHLORATI ÆTHEREA—ethereal tincture of the perchloride of iron, known formerly under the name of Bestuscheff's nervine tincture. This is prepared by adding ether and alcohol to a solution of the perchloride of iron. Part of the ferric chloride is thereby reduced to ferrous chloride, and some of the alcohol is oxidised into aldehyde. The tincture is a clear yellow fluid with an ethereal odour, and has a burning and at the same time a ferruginous taste. It contains 1 per cent. of iron. The dose is from ten to thirty drops.

AMMONIUM CHLORATUM FERRATUM—ammoniated iron. A reddish-yellow powder which absorbs moisture on exposure to the air, is readily soluble in water, and contains about 2·5 per cent. of iron. It is decomposed by exposure to light and air, certain oxides being formed which are almost insoluble. The salt is prepared by heating together a solution of perchloride of iron with ammonium chloride, and evaporating to dryness. It is best given in the form of pills, in doses from 0·1 to 0·5 gramme (about 1½ to 8 grains).

It frequently happens that when the administration of iron is urgently required, the stomach will not tolerate the smallest doses of the remedy, even when given in what is probably its mildest form, namely, the natural chalybeate waters. It exists in these waters chiefly as ferrous carbonate dissolved in a large excess of carbonic acid, and in this form is very readily absorbed.

Lunatics also, suffering from chlorosis, sometimes refuse to take the remedy.

In such cases we may have recourse to SUBCUTANEOUS

INJECTIONS,[1] and apparently with good results. Very much, however, depends on the choice of a suitable preparation. A considerable number of experiments on animals have been made with regard to this. It was first demonstrated in rabbits,[2] that citrate of iron when injected does not give rise to abscesses and is readily absorbed.

In these experiments the iron was eliminated by the kidneys and the liver; the pancreas, stomach, intestines, and salivary glands taking no part in the process. Ferric and ferrous oxide, the former predominating, were found in the blood-serum and in the serum of the peritoneal cavity, in from one to six and a half hours after the injection of these substances, but no trace of them could be found in the aqueous humour. The experimenter inferred from this that iron exists in the body only in combination with albumen, and that as the aqueous humour contains no albumen, iron could consequently not pass into it.

The glomeruli of the kidneys were free from iron, which, however, was present in the convoluted tubules. If a ferric salt was injected, deposits consisting of a slightly granular and delicate reticulum were found in these tubules, whilst if a ferrous salt was given the deposits appeared more as flakes and shreds in the lumen of the tubules. In any case, it was evident that the iron was excreted by the epithelium of the convoluted tubules.

Human beings readily tolerate these subcutaneous injections, especially when they are made in THE BACK. A ten per cent. solution of citrate of iron is the most useful, and must be quite free from turbidity. For adults 1 c.cm. (about 16 minims) of this solution may be employed, and 0·5 c.cm. (about 8 minims) for children. Even with these doses, traces of iron could be detected in the urine, on the addition of ammonium sulphide. After smaller doses no traces of iron could be detected, whilst larger doses appeared to act injuriously. Satisfactory results were obtained by these injections in a series of ten patients. In the case of a

[1] Eulenberg, 'Berl. klin. Wochenschr.,' 1883, No. 2; W. Nasse, 'Zeitschr. f. Psychiat.,' 1885, Bd. xli, S. 526.

[2] Glaevecke, 'Arch. f. exper. Path. u. Pharmak.,' 1885, Bd. xvii, S. 466.

chlorotic girl the amount of hæmoglobin, which at the commencement of the treatment was only 38 per cent. of the normal, was increased by fifty-four injections to 82 per cent. At the same time the body-weight of the patient increased by 8 kilogrammes (about 17½ lbs.); the menstrual discharge, which had been suppressed for several months, was re-established, and a hæmic murmur in the pulmonary artery disappeared. In another case of marked anæmia, after hæmatemesis, associated with a feeble pulse, œdema, and considerable ascites, a few injections were followed by a remarkable diuretic effect; the dropsy quickly disappeared, and the patient rapidly recovered. Again, a pregnant woman suffering from severe anæmia was cured in fourteen days by repeated injections of a 1 per cent. solution, of which 1 c.cm. (about 16 minims) was daily injected in the gluteal region.[1] The injections caused a slight burning pain, and the place of injection was still somewhat sensitive to the touch twenty-four hours later, but this was all, and neither swelling nor abscess occurred in any case. The FERRUM CITRICUM OXIDATUM, citrate of iron, $Fe_2(C_6H_5O_7)_2 + 6H_2O$ of the German Pharmacopœia, consists of thin ruby-red transparent scales, which have a slightly chalybeate taste and an acid reaction, and contain from 19 to 20 per cent. of iron. The salt dissolves completely though slowly in cold water.

It has been suggested that when iron is injected into the subcutaneous cellular tissue, the rapid absorption of it, by the blood and lymph, which necessarily takes place may give rise to symptoms of poisoning.[2] This, however, is no new discovery, for we have long been familiar with such symptoms in individuals who have taken iron for too long a time, or in excessive doses, as well as in animals into which too large a quantity has been injected. Every physician is

[1] Mori, 'Centralbl. f. Gynäkol.,' 1886, S. 367; H. Neuss, 'Zeitschr. f. klin. Med.,' 1881, Bd. iii, S. 1; S. Graber, 'Zur klin. Diagnostic d. Blutkrankheiten,' Leipzig, 1888, S. 47 u. 61.

[2] Orfila states that some dogs died with all the symptoms of inflammation of the stomach and bowels, and with general paralysis, twelve, fifteen, or twenty-seven hours after powdered sulphate of iron had been sprinkled on the exposed cellular tissue of the thigh.—'Lehrb. d. Toxikologie,' 1853, Bd. ii, S. 38.

acquainted with the symptoms which arise when young girls have taken large doses of iron for some time. Irritation of the abdominal organs, which evidently begins in the intestine, is set up, and may extend to the peritoneum, and be accompanied with the usual symptoms, pain, discomfort, a tendency to vomit, diarrhœa or constipation, and general exhaustion,—the last, however, not being apparently dependent upon the condition of the abdominal organs. These symptoms may persist for some days even when the iron is immediately discontinued, and may then gradually subside.

A case was published from the clinic at Kiel, in which the injection of so small a dose as 0·2 gramme (3 grains) of citrate of iron produced general discomfort, followed in thirty minutes by vomiting, and weakness which lasted for some hours. In another case violent diarrhœa supervened, but this soon subsided.

Dilute solutions of citrate of iron increased the secretion of urine, whilst concentrated solutions, subcutaneously injected, diminished the secretion to a marked extent, induced strangury, and brought about the death of the animal.[1] Inflammation of the stomach, intestines, and kidneys, and paralysis of the central nervous system, may therefore be caused by introducing iron into the system either too rapidly, or in excessive quantities. The practical conclusions to be drawn from the above are self-evident. It is especially necessary to exercise caution, when administering the remedy hypodermically.

We will now turn to the consideration of phosphorus, which at the present day is supposed to have therapeutic properties closely allied to those of iron. It was discovered by Brandt of Homburg in 1669, in the course of some alchemistic endeavours to prepare a tincture, from the urine,

[1] Cl. Bernard, 'Arch. génér. de méd.,' 1848 (quoted by Kölliker and Müller).

which was to convert the baser metals into gold. Although the discovery was not divulged for some time we find that phosphorus was employed medicinally within seven years, as may be inferred from the title of the following book—J. S. Elsholz, 'De Phosphoris: Observations Quatuor, Berolini,' the second edition of which was published in 1681. The publications on its therapeutic effects were not at first very numerous, but a considerable number appeared in the following century, whilst they ceased altogether in Germany so soon as it was recognised how poisonous were the effects produced by the action of phosphorus upon the workmen engaged in the manufacture of lucifer matches. Attention was now solely directed to the poisonous effects produced by the substance; the terrible results as seen in necrosis of the jaw from the action of phosphorus, together with the unusually frequent murders and suicides which were effected by means of the detached heads of the matches, led to its being regarded simply and solely as an "absolute poison" —the term applied to it not many years since by a practical physician; as if such a thing as an absolute poison existed! —which should be completely banished from the domain of rational therapeutics.

In 1872 G. Wegner[1] published the results of a series of experiments which, apart from their great therapeutic interest, were possibly designed to put the matter in a different light, so soon as it could be discussed in an unprejudiced way.

The task which Wegner undertook, was to determine what effects were produced by phosphorus when it was given to animals for weeks or months in doses too small to produce any poisonous effects.

He first investigated the effects of the fumes of phosphorus. He found that rabbits which were kept for several weeks in a room filled with the fumes bore the poisonous atmosphere without any untoward results as soon as the initial bronchial irritation had passed off. The skull bones showed on maceration some extremely fine osteophytic deposits in the periosteum in the neighbourhood of the nasal cavities. Some-

[1] G. Wegner, "Der Einfluss des Phosphors auf den Organismus," 'Arch. f. pathol. Anat.,' &c., 1882, Bd. lv, S. 11, with three plates.

times a swelling was observed in the upper or lower jaw. The bones were enlarged, the soft parts thickened by caseous infiltration, and the jaws became immoveable. Periostitis, with the formation of coarse bony tissue and subsequent necrosis, was found on dissection. This was especially noticeable when there was erosion of the teeth or of the mucous membrane, whether produced accidentally or intentionally.

The periostitis of the jaw depended upon the localised action of the fumes. It was never produced when phosphorus was mixed with the food; in fact, wounds of the mucous membrane extending right down to the periosteum healed just as quickly in animals which were taking phosphorus as in those which were under perfectly normal conditions. The fumes of phosphorus have, therefore, some specific irritating action on the periosteum, when brought directly in contact with it. Phosphorus fumes also developed marked hyperosteosis in the tibiæ of rabbits when the periosteum was exposed.

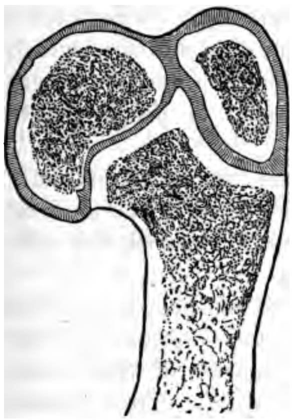
Wegner then experimented upon young rabbits, fowls, cats, dogs, and a calf, giving them pills in which the dose of phosphorus was so small that apparently no change was produced in the general condition of the animals. The skeleton, however, after a few weeks presented some remarkable changes, especially when compared with the skeletons of similar control animals to which no phosphorus was given.

In all parts where, physiologically, spongy osseous tissue is usually developed from cartilage, it was found that, instead of the normal largely cancellated osseous tissue containing abundance of red marrow, a certain tissue was developed, which appeared to the naked eye perfectly uniform, firm and hard, similar to that of the surface of the long bones. This was also the case in the epiphyses and apophyses of the long bones, in the vertebræ (including those of the cranium), in the ribs, the shoulder-blades, the carpal and tarsal bones, the pelvis, &c.

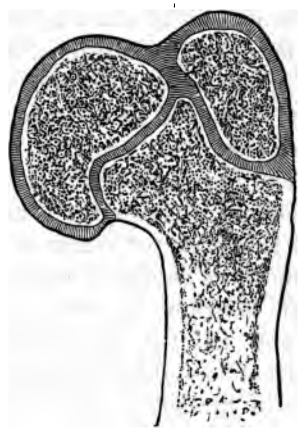
This change was especially well marked in a longitudinal section of the humerus of a calf, to which phosphorus had been given for a period of eight weeks (see figure P).

"We see here a very large zone of apparently compact

ossification, stretching downwards from the intermediate cartilage of the upper epiphysis, and a narrower zone from the lower intermediate cartilage stretching upwards to



P



N

the lower epiphysis, the head of the humerus, and to the greater tuberosity, and affecting the whole surface of the cartilage." The change which has taken place is in striking contrast to the normal condition as depicted in figure N.

On microscopical examination this deposit, caused by the action of the phosphorus, is seen to consist of true bone.

If the administration of the phosphorus was continued, a further compact osseous deposit took place in the cartilaginous extremities of the long bones, whilst the existing spongy tissue was disintegrated in order to form a medullary cavity. Later on the "artificially" formed bone itself was also partially disintegrated in order to form a medullary cavity. An obliteration of the medullary cavity with osseous deposit in young growing animals cannot, therefore, be produced by the action of phosphorus.

The thickening of the PERIOSTEUM and of the sutures of the flat bones is very similar to what takes place in sclerosis, and the changes are easily recognised under the microscope. The Haversian canals are considerably diminished in diameter, but never completely obliterated. On comparing the long bones of growing animals to which phosphorus has been given for some months, with those of animals which

have been for a similar period under normal conditions, we observe in those bones having the same circumference, a marked thickening of the shaft at the expense of the diameter of its medullary cavity, such as is depicted in the sections which I place before you, of a femur of a young rabbit under normal conditions, and the femur of a rabbit to which phosphorus had been given. The laminated cranial bones are also thickened in a corresponding manner in proportion to their size.

The development of the bones of the fœtus was distinctly increased when phosphorus was administered to the mother, but this does not occur in young animals fed with the milk of mothers similarly treated.

G. Wegner, by giving phosphorus to full-grown fowls for several months, succeeded in completely obliterating the original medullary cavities by the formation of true bone, and in rendering the bone perfectly solid. This process was first completed in the tarsal bones, then in the tibia, the bones of the forearm, the femur, and the humerus.

A chemical analysis of the bone produced by the action of phosphorus showed that it did not differ essentially from the normal conditions, either in its inorganic or its organic constituents, nor did it contain a preponderance of phosphorus, as might have been theoretically expected (Gad). It appears, therefore, that this process was not a morbid one, but merely consisted in an extension and acceleration of the normal processes.

Wegner himself at once applied these important results to therapeutic use, and with very good results. He fractured the limbs of animals, and performed subperiosteal resection, and also transplanted the periosteum. In these cases he always found that the administration of phosphorus caused the injured periosteum to develop a larger amount of bone, and of a denser quality. The callus more especially of the fractures had a perfectly ivory-like appearance. It seemed, therefore, that the formation of new bone received a considerable temporary stimulus from the administration of phosphorus. In short, it was very evident that phosphorus, when introduced into the blood in small quantities, stimulated the activity of the bone-forming tissues.

The first in Germany—so far as I can ascertain from the literature of the subject—to test the above-mentioned results on the human subject was Dr. Friese.[1] He had to treat three children, nearly at the same time, who were suffering from RICKETS. The children were exhausted by diarrhœa, and had lost all their fat; some of their bones were curved; the abdomen in each case was very prominent, and the general condition of the children was extremely pitiable. All known remedies had failed to produce any beneficial effect. Friese prescribed albuminate of iron, to which, reasoning from Wegner's results, he added very small doses of phosphorus. The emaciation of the children diminished, the folds of the skin disappeared being filled up with fat, the wrinkled and aged-looking face became smooth, the abdomen less prominent, and the yielding bones were strengthened. These results induced Friese, in treating adults who were simply suffering from chlorosis, always to combine a small dose of phosphorus with the iron. This mode of treatment, he says, has in his hands proved highly satisfactory.

OSTEOMALACIA afforded another opportunity for the therapeutic application of the facts discovered by experiments upon animals. W. Busch,[2] of Bonn, has published the following results.

The disease showed itself after her third confinement, in a peasant's wife, thirty years of age, of fairly healthy appearance. I saw her six months after the birth of the child, when she complained on standing and walking, of great pain, which had latterly increased to such an extent that she was only able with great difficulty to get from her bed to a chair. It was noticed that both when standing and when walking her legs were in close approximation. No alteration was observable in any of the skeletal bones, with the exception of those of the pelvis, where, in a comparatively short time, very considerable changes had taken place. The pelvis seemed to be compressed laterally, the symphysis pubis projected forwards, the horizontal ramus being bent and

[1] Friese, 'Berl. klin. Wochenschr.,' 1877, S. 420.

[2] W. Busch, 'Sitzungsber. d. Niederrhein. Ges. f. Nat. und Heilk.,' May 16th, 1881; 'Berl. klin. Wochenschr.,' 1882, S. 10.

angular. I prescribed rest in the horizontal posture for three months, and Wegner's phosphorus pills. When I again saw the patient at the end of this time she was able to stand and walk with greater security, but had not improved sufficiently for the treatment to be altered. After another two months she was able to go upstairs without help, could move about freely, and said she felt no further discomfort. On investigation I found that there was no change in the distorted condition of the pelvis, but the remaining bones of the skeleton retained their normal shape.

The second case was more complicated, and therefore more interesting, and I was able to keep it under observation for a longer time. A woman fifty years old had suffered from time to time from severe pain in the right upper arm, which came on spontaneously, and was also caused when pressure was made below the insertion of the deltoid muscle. As there was no change with regard to the thickness, shape, or direction of the humerus, I regarded it as a case of endosteitis, painted the spot with iodine, and prescribed potassium iodide and calcium salts internally, together with the use of alkaline baths. No improvement, however, took place in the condition of the patient, and after some weeks she discontinued the treatment. About nine months later I was again called to the patient, and was astonished at the changes which had taken place during this period. At no time was the patient particularly well nourished, but now she was wasted to a skeleton. She was entirely confined to her bed, and could only stand or take one or two steps with difficulty when both her shoulders were supported, her legs at the time being closely adducted. In addition to this she looked at least half a head shorter than formerly, for she had become markedly hunch-backed, and this, together with lordosis of the cervical vertebræ, gave her head the appearance of having sunk between the shoulders. The clavicle and ribs were distorted, and the thigh was bent, so that both the normal curvatures of the femur were greatly exaggerated; at the same time there was very great deformity of the pelvis, the sides of the ilia being laterally compressed, and the symphysis pubis projecting forwards. It was remarkable that the humerus, in which the first subjective sym-

ptoms had appeared, showed no perceptible change. The patient now took Wegner's phosphorus pills for a year and a half, with the exception of a few short intermissions. After the first month of this treatment she was still completely bedridden, after about seven months she was able to walk a few steps with the help of a crutch, and for the last two years she has been able to move about freely, but she presents the same deformed appearance as at the commencement of the treatment. Owing to the contracted condition of the chest from the distortion of the body, heart disease has been developed; but the bones, instead of being soft and useless, are now hard and serviceable.

Such is the statement of W. Busch. The following observations of M. Kassowitz,[1] of Vienna, on the treatment of RACHITIS with phosphorus, are of more recent date.

This author has, since the year 1879, treated 560 cases by phosphorus. The shortest period for which the drug was given was at least a month, whilst most of the patients took it for several months, and during this time all were carefully watched. The patients were children of from one to eight years of age, but most of them were about two years old. Kassowitz states that the results, in all the cases in which phosphorus was given regularly, were so favorable, that they surpassed his most sanguine expectations. The good effects of the remedy were shown most distinctly in the cranial bones, for cranio-tabes, with the fontanelles widely open, was cured in four to eight weeks. The same was true of spasm of the glottis. The effect of phosphorus on the ribs and vertebræ was somewhat less striking, though still distinctly marked. Its effect was most pronounced in the severe cases of children several years old, who had either lost or had never acquired the power of standing upright and of walking alone. Among other beneficial results which are mentioned are easier dentition, and a general improvement in the nutrition of the patient.

These results have been confirmed by further experience

[1] M. Kassowitz, 1, 'Versamml. d. Gesellsch. f. Kinderheilk. Naturf. und Aerzte-Vers. zu Freiburg i. B.' 1883, Leipzig, 1884, S. 77; also 'Jahrb. d. Kinderheilk.,' 1885, Bd. xxiii, S. 352; 'Wien. med. Wochenschr.,' 1889, No. 28, *et seq.*

during the last twelve years.[1] The improvement is obvious in young patients, although no alteration may be made in their food, place of abode, or mode of life. In the first place, the fits of laryngeal spasm and eclampsia become milder, and then disappear in one or more weeks; improvement in the general nutrition soon follows, and later on the bones become firmer. On the other hand, negative results have also been published, and the treatment with phosphorus absolutely condemned. But, considering how generally the beneficial action of the drug has been confirmed, these negative results must have been due either to the phosphorus being administered in an unsuitable form, or the dose being too small, or to the treatment not being continued for a sufficient length of time. In the Children's Clinic here at Bonn, and at the Veterinary Institute at Berlin, the beneficial action of the remedy has been further corroborated.

Commercial phosphorus consists of white or yellowish, wax-like, semi-transparent, cylindrical masses. It melts under water at 44° C. (111·2° F.), and when exposed to the air emits white vapours, having a characteristic odour. It readily takes fire, and is luminous in the dark. When it is kept for some time it becomes red, and sometimes also black. It is insoluble in water, but dissolves readily in carbon bisulphide (CS_2). It is only slightly soluble in fatty and ethereal oils, alcohol, and ether. It must be kept under water and protected from the light. The Pharmacopœia gives the maximum dose at 0·001 gramme (about $\frac{1}{60}$ grain), and the largest amount to be given in a day at 0·005 gramme (about $\frac{1}{12}$ grain).

Oleum Phosphoratum, prepared by warming one part of phosphorus in eighty parts of sweet oil of almonds, was once officinal. A solution of this kind is still employed, and is sometimes prescribed in gelatine capsules on account of its

[1] Soltmann, 'Breslauer ärztl. Zeitschr.,' 1884, No. 9; Penzoldt, 'Lehrb. d. klin. Arzneibehandlung,' 1889, S. 56; L. B. Mandelstamm, 'Jahrb. f. Kinderheilkunde,' 1890, Bd. xxx, Heft 4; M. Cohn, ibid., 1894, Bd. xxxvii, Heft 2; Fröhner, 'Lehrbuch d. Arzneimittellehre für Tierärzte,' 1890, S. 354; Ungar, 'Correspondenzbl. d. Aerzte-Vereins in Rheinland und Westfalen,' 1890, No. 46; Sternberg, 'Wiener. med. Woch.,' 1892, No. 44 (Osteomalacie).

disagreeable taste. Chemists keep this ready prepared for the sake of convenience, and so the physician must take care not to have an oily solution dispensed which has stood for some time, for then the phosphorus falls to the bottom of the vessel as a RED PRECIPITATE, and the preparation is of course useless. For the same reason pills which have been kept some time, or which have not been coated, should not be employed. In either case the phosphorus may have become oxidised or volatilised, or the pills may have become as hard as stone, and will then, as is sometimes the case with other pills, pass through the intestine undissolved.

M. Kassowitz, in prescribing for rickety children, formerly began with 0·001 gramme (about $\frac{1}{60}$ grain) daily. He afterwards found that 0·0005 gramme (about $\frac{1}{120}$ grain) was sufficient, and is now in the habit of giving this amount once daily. He used a solution of one part of phosphorus in ten thousand parts of oil, or some similar emulsion, giving a teaspoonful once a day. E. Hagenbach,[1] of Basel, gave 0·0005 to 0·002 gramme (about $\frac{1}{130}$ to $\frac{1}{30}$ of a grain) daily in the form of the following emulsion :—0·01 part of phosphorus dissolved in 10 parts of oil, to which 5 parts of gum acacia, 5 of sugar, and 80 of water were added. One to four teaspoonfuls of this were given in the course of the day.

The solution must be kept in a cool place, and protected from the light, otherwise the phosphorus is thrown down as a red precipitate which possesses no active properties.

Physicians in former times used, in cases of rickets, scrofula, and atrophy in children, to prescribe hartshorn shavings, Cornu Cervi Raspatum, which consist, like all other bony substances, chiefly of CALCIUM PHOSPHATE. They also prescribed CORNU CERVI USTUM, which of course contains a larger percentage of calcium phosphate.

In place of these antique preparations, we now have recourse to the pure calcium salt obtained by the ordinary chemical methods.

Calcium phosphate, the CALCIUM PHOSPHORICUM of the German Pharmacopœia, is a light, white, crystalline powder, insoluble in water, but soluble in dilute hydrochloric

[1] At the Kinderhospital in Basel (see the Doctordissertation of J. de Montmellin, 1888).

acid. It is prepared by the double decomposition of calcium chloride and sodium phosphate, $CaCl_2 + Na_2HPO_4 = 2NaCl + CaHPO_4$, with which are combined two molecules of water of crystallisation. This preparation is also known under the name of superphosphate of lime.

The administration of calcium phosphate was recommended by Beneke, on the ground that in the chronic disorders of childhood, to which reference has already been made, this salt is, from some special cause as yet not made out, excreted in large quantities in the urine. According to his view there was, in these disorders, a pathological deficit of this compound in the system, and by an artificial supply of it the normal process of tissue formation might be assisted.

The point has been denied, confirmed, and experimentally investigated, but as yet has not been settled. A definite conclusion can only be arrived at after a long series of clinical observations and investigations have been made on human subjects. This as yet has not been done. The results obtained from experiments on healthy animals are very valuable as a starting-point for the inquiry, but nothing more. The conditions under which they were obtained are very different from those with which we are concerned in human beings. This has been already experimentally shown, for in rabbits a large amount of the phosphate added to their food passes into the circulation and is excreted by the kidneys, whereas in dogs only a very small portion passes into the circulation, the rest passing off entirely in the fæces. This is also the case with regard to human beings.

A hundred parts by weight of dried human bone contain about 84 per cent. of calcium phosphate and about 1 per cent. of magnesium phosphate. These phosphates are indispensable constituents for the formation of new cells. It is therefore conceivable that, in cases where an increased elimination of these salts takes place, their administration in excess may act beneficially on the tissues involved. We will not here stop to discuss whether or not this is possible.

The dose of the officinal salt is from 0·2 to 0·5 gramme (3 to 7½ grains), and may be given in combination with

some preparation of iron, calcium carbonate and a vegetable bitter, after meals.

If phosphorus is administered in larger doses than those mentioned in the previous section, which have been determined with great care, symptoms of its POISONOUS effects soon show themselves. Its irritant action on the stomach produces pain, tenderness, vomiting, distension, &c. These symptoms persist, if the dose has been moderately large, even after the remedy has been discontinued. In severe cases, after the vomiting has ceased, the patient may for a few days apparently suffer no discomfort. He then becomes JAUNDICED, pain returns in the region of the stomach, and is felt over an extended area. By percussion we find that the liver is enlarged, there is general discomfort, with aching and pains in all the limbs. The pulse is small and fast, the heart sounds soft and accompanied by a murmur.

The symptoms now increase in intensity. There is hæmorrhage from the bowels, the nose, the uterus, and the skin. The mind often remains clear to the last; sometimes there is violent headache, and, as a rule, drowsiness. In a few instances convulsions, delirium, and maniacal excitement have been observed. The temperature may fall as low as 32° C. (89·6° F.), or rise as high as 41·5° C. (106·7° F.). The urine is scanty and contains bile and albumen, and subsequently fatty casts, broken-down cells, and blood. In 21 cases reported by Riess[1] in which the date of the poisoning could be accurately fixed, the length of

[1] Riess, 'Real-Encyklopädie d. ges Heilkunde,' 1882, Bd. x, S. 554. My statements are taken from the clear description given by this author of the symptoms and morbid anatomy associated with this form of poisoning. As regards its medico-legal aspects reference can be made to the exhaustive account by Schuchardt in Maschka's Handbuch, 1882, Bd. ii, S. 176—228; see also Tardieu, 'L'Empoissonnement,' 1875, pp. 476—616.

time which elapsed before death, varied from three to fourteen days, the average being $7\frac{1}{2}$ days. Even in severe cases recovery sometimes took place, but the convalescence then occupied several weeks. Sometimes death occurred within a few hours after taking the phosphorus. This happened when unusually large doses were given,—such, for instance, as 0·3 gramme (4·5 grains) to a child seven weeks old.

As we have seen, the symptoms of poisoning may vary very considerably according to the dose and the mode of its administration, and in many cases may not be very readily recognised without further evidence. The symptoms of irritation of the abdominal organs, the collapse or excitement of the nervous centres, the gradual failure of the heart's action, may each be either very pronounced, or, on the other hand, may be entirely absent.[1] The post-mortem appearances enable us to arrive much more easily at a correct diagnosis.

Numerous HÆMORRHAGIC EXTRAVASATIONS, together with FATTY DEGENERATION of the glandular organs, are the characteristic signs.

The amount of hæmorrhage varies from the smallest petechiæ to complete effusion. The latter is most frequently found in the peritoneum, and in the cellular tissue beneath the skin and between the muscles of the trunk and legs. Hæmatoma of the ovaries is frequently observed. The coats of the smaller vessels throughout the body are the parts first affected by the phosphorus as it circulates through the system, and the hæmorrhage results from the fatty degeneration of these vessels.

The fatty degeneration of the liver, which is usually very considerably enlarged, is most striking.[2] This organ has a yellow appearance both internally and externally, and a firm and doughy consistence. On examining the tissues microscopically the cells appear to contain either numerous minute fatty globules, or a few large ones, apparently from

[1] C. Tüngel, "A rapidly Fatal Case of Poisoning by Phosphorus, without Gastro-enteritis or Jaundice," 'Arch. f. pathol. Anat.,' 1864, Bd. xxx, S. 270.

[2] G. Lewin, 'Arch. f. pathol. Anat.,' 1861, Bd. xxi, S. 506; Saikowsky, ibid., 1865, Bd. xxxiv, S. 73.

the coalescence of the former. At the same time the cells are not destroyed, as was formerly supposed to be the case; for after digesting the section in ether, which dissolves out the fat, both the cells and their nuclei can be distinctly seen (Ebstein and Riess). The interstitial connective tissue may become so hypertrophied as to cause granular atrophy of the whole organ. The connective tissue of the stomach is also hypertrophied, a condition associated with indurated gastritis.

Neither erosions nor commencing ulceration exist in the stomach, but there is extensive cloudy swelling of the whole glandular layer, constituting a true gastritis glandularis or gastradenitis.[1] The mucous membrane is somewhat thickened, and appears consequently opaque and white, yellowish white, or slate-grey. The villi and glands in the small intestines, as well as the pancreas, have also undergone degeneration. These effects are not produced by the direct action of the phosphorus, for they are also developed in animals when the poison is introduced into the rectum or under the skin; but they nevertheless are caused by the phosphorus which, dissolved in fat, circulates through the system, and permeating the glands, acts upon their living protoplasm.

As a rule, there is fatty degeneration of the heart, the kidneys, and of the muscles generally, but especially those of the abdomen and thigh. The viscera of newly born animals, to the mothers of which moderate doses of phosphorus had previously been administered, presented the same degeneration of the vascular coats, the gastradenitis, and the fatty degeneration of the liver, as were observable in the viscera of the parent.[2]

The red blood-corpuscles in the human subject do not appear to undergo any change.[3]

[1] Virchow, "Der Zustand des Magens bei Phosphorvergiftung," 'Arch. f. path. Anat.,' 1864, Bd. xxxi, S. 399; H. Senftleben, ibid., 1866, Bd. xxxvi, S. 520; M. Bernhardt, ibid., 1867, Bd. xxxix, S. 23; Ph. Falck, ibid., 1870, Bd. xlix, S. 457; Hoffmann, 'Vierteljahrschr. f. ger. Med.,' 1870, Bd. xii, S. 201.

[2] J. M. Miura, 'Arch. f. pathol. Anat.,' 1884, Bd. xcvi, S. 54.

[3] W. Dybkowsky, 'Hoppe-Seyler's Untersuchungen,' 1866, S. 55; C. v. Noorden und G. Badt, in the Doctordissertation of the latter, Berlin, 1891, S. 49.

The numerous experiments on animals (and, so far as the pathological changes are concerned, you have an illustration in the body of the dead rabbit here placed before you) have added little, from a toxicological point of view, to the knowledge we already possess from the exhaustive observations which have so frequently been made on the human subject. The production of nervous excitement and narcosis by the poison might, judging from the experimental results only, be called in question because, although these symptoms may be very distinctly manifested in the human subject, they are not developed in the insensitive brains of rabbits and guinea-pigs.

From a pharmacological point of view, the following few details are of importance. Kassowitz, in repeating Wegner's experiments, gradually increased the doses of phosphorus until he very quickly arrived at a point when the bony deposit no longer acquired greater density, but, together with a considerably increased development and dilatation of the vessels supplying the bones and cartilages, the medullary spaces were correspondingly increased and enlarged. Further, osseous tissue of a very vascular, light, and spongy character was formed in the medullary cavity, and under the periosteum, so that the bones presented all the characters of rickets. In fowls, by giving still larger doses, the morbid vascularity at the ends of the long bones was developed to such an extent that from the increased absorption of bone and cartilage complete separation took place of almost all the epiphyses from the shafts of the bones, just in the same manner as occurs in fully developed syphilitic osteochondritis. These symptoms, too, were developed without the calcium salts in the food being in any way diminished.

Tiedemann,[1] Munk, and Leyden,[2] besides others, have seen animals exhale "clouds" of white luminous vapour from the nostrils and mouth, after the introduction of phosphorus dissolved in oil into their circulation. For some time afterwards the breath, when exhaled, had the odour of phosphorus. This resulted from the oil drops being occluded in

[1] Tiedemann, 'Zeitschr. f. Physiol.,' 1835, Bd. v, S. 221.

[2] Munk und Leyden, 'Die acute Phosphorvergiftung,' Berlin, 1865.

the pulmonary capillaries, and the phosphorus being there oxidised by the air. If the oil is emulsified so that the particles are not larger than a blood-corpuscle, this exhalation of phosphorous acid vapours does not take place, and the animal dies with the same symptoms as occur when the poison has been swallowed.[1] In the latter case, however, the internal organs smell of phosphorus, and are luminous in the dark.

When phosphorus is taken internally it increases the albuminous waste in the system, and consequently the amount of nitrogen excreted in the urine, very considerably, the latter sometimes as much as threefold. This increase is fairly proportionate to the increase in the severity of the symptoms resulting from the poison.[2] It clearly depends upon the disintegration of albumen in the system. The absorption of oxygen is diminished.

The fatty degeneration of the different organs is the result of the morbid disintegration of the cells. Nitrogen is given off, and with a small amount of carbonic acid, passes off as urea, &c., whilst the non-nitrogenous residue is retained unoxidised in the system. If phosphorus in poisonous doses be administered to animals that have been kept without food, the amount of fat in the liver increases, whilst that in the rest of the body diminishes.[3] Death results from paralysis of the protoplasm of the internal organs, which is brought about by this rapid degeneration of the cells.

In what way do the foregoing statements help us to explain the therapeutic and poisonous action of phosphorus?

We are tempted in the first place to attribute the former to the additional supply of phosphoric acid to the cells of the nervous system and to the bones, but this idea is simply not tenable, for the amount of phosphorus is too small, and is absolutely insufficient to replace the large deficit. The cautious employment of the vapours of phosphorus in order to stimulate the formation of bone distinctly demonstrates

[1] L. Hermann, 'Arch. f. d. ges. Physiol.,' 1870, Bd. iii, S. 1.

[2] J. Bauer, 'Zeitschr. f. Biologie,' 1871, Bd. vii, S. 63; C. v. Noorden u. G. Badt, loc. cit., S. 32.

[3] Finkler, quoted in W. Schmitt's Dissertation, Bonn, 1885.

that THE STIMULATING EFFECT which leads to increased growth is essentially a LOCAL one. This localised stimulation may also occur when the remedy is given internally. In cases of poisoning by phosphorus its presence can be actually demonstrated in the viscera; it is also possible for it, when dissolved and protected from oxidation by the fat in the intestines, to pass from them to the other viscera. In this way it comes into direct contact with the living protoplasm. But before proceeding further with my explanation let me give you a few experimental facts.

A small piece of phosphorus was introduced under the skin of a warm-blooded animal, and allowed to remain there, the wound being carefully sewn up. After several days the wound was reopened, and found to be free from any inflammatory action, or at most to show only slight suppuration; there was no evidence of any caustic action.[1]

A fragment of phosphorus 2·5 cm. long and 2 mm. thick was passed through a small opening well into the peritoneum of a rabbit; the edges of the peritoneal wound were then sewn together by catgut with all antiseptic precautions. Three days later the animal was found to be paralysed and unconscious. The post-mortem examination, made immediately after it was killed, showed that the edges of the wound in the peritoneum were closely united; at the spot where the phosphorus was located there was a thin layer of pus, in the peritoneal cavity there was no abnormal amount of fluid; the peritoneum itself was smooth and glistening, and nowhere was any trace of morbid congestion apparent. The phosphorus was found lying upon the transverse colon; at the spot where it lay there was a depression corresponding with its size, but beyond this no change was observable in the wall of the intestine. The lungs were red and gelatinous, more especially at their bases; the heart continued to beat for twenty minutes after the thorax was opened; the liver was brownish yellow with bright yellow edges, and under the microscope the cells showed advanced fatty degeneration; the appearance of the stomach was normal, but there was considerable congestion of the intestines.

[1] L. Ranvier, 'Compt. rend. de l'Acad. des Sc. et mémoires de la Soc. Biol.,' 1866.

This is one experiment out of many[1] which confirm and amplify the above-mentioned statement of Ranvier. Phosphorus which is not undergoing oxidation only acts as a caustic on glandular protoplasm, or on tissues containing it.

There is, as is well known, a modification of the yellow crystalline phosphorus which is insoluble in fat, does not ignite on exposure to the air, and does not develop ozone, but which gradually in damp warm air undergoes the same changes as the yellow, and may also, when heated to 260° C., be reconverted into the ordinary form. Some of this red amorphous phosphorus, which is without any poisonous properties, was suspended in water in a finely powdered state, and then injected into the jugular vein of various animals;[2] during the first few days the animals appeared to be perfectly healthy; they then became languid, ceased to eat, and, as a rule, died after six or eight days. Post-mortem examinations invariably revealed fatty degeneration of the liver, particularly in patches, in the middle of which small bits of phosphorus, varying in size, could be distinctly recognised. Finely pulverised charcoal injected in a similar way produced no effect whatever. In frogs the red phosphorus produced no poisonous effect, "presumably because it was transformed too slowly at the very low temperature of this animal."

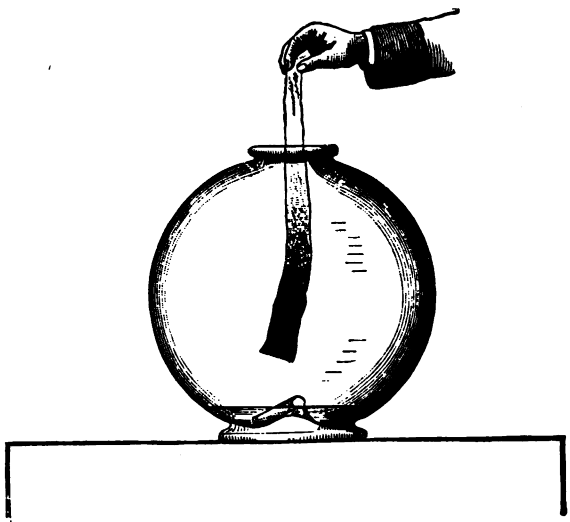
The fatty degeneration appears, therefore, to depend altogether upon the direct contact of the phosphorus with the living protoplasm. Other chemical bodies which have a strong oxidising or reducing action also induce fatty degeneration of the cells, and paralysis of their specific functions. Everything which contains oxygen in an active form or which can cause it to become active—and phosphorus is a body of this nature—will produce these changes very rapidly.

I have here a large glass jar which contains a little water.

[1] C. Binz und C. Schubert, in the thesis of the latter for the doctor's degree,—'Experimentelle Beiträge zur Toxikologie des Phosphors und des Arseniks,' Bonn, 1889, S. 16.

[2] O. Nasse, 'Naturforsch. Ges. zu Rostock,' May 16th, 1885; see also J. Neumann, 'Experim. Studien zur Phosphorvergiftung,' Doctor-dissertation, Rostock, 1886, S. 6.

In this is placed, but not entirely submerged, a stick of yellow phosphorus. The jar and its contents have been in a warm room for several hours. If now I dip a broad piece



of filtering-paper moistened with mucilage of starch containing potassium iodide, into the jar, the paper immediately turns blue, for the air in the jar contains ozone, by which the potassium iodide is decomposed in the usual manner. The formation of the ozone may be represented by the following equation: $2P+3O_2=P_2O_3+3O$, the phosphorus anhydride P_2O_3 combining with the water and remaining in solution as phosphorous acid, $P_2O_3+3H_2O=2H_3PO_3$.

There is no manifest reason why phosphorus, when it has been introduced into the circulation, should not be transformed in a similar way, by the oxygen of the hæmoglobin.

It is immaterial whether in these changes we regard the active atom of oxygen in ozone as a strong oxidising or as a powerful reducing agent; as is well known, ozone can, according to circumstances, act in either way. Neither does it matter if we attribute the changes to the intermediate formation and rapid oxidation of phosphoretted hydrogen,

the action of which is said to be very similar to that of finely divided phosphorus.[1] The mode of action may vary in some details, but the conclusion to which I have arrived is, that the changes in the system produced by phosphorus result from the development of active oxygen through the agency of that substance.

We have further to notice that the oxides of phosphorus are either not poisonous, or if they are, the effects they produce differ both as to their nature and intensity from those of phosphorus itself.[2]

If this unusual liberation of oxygen within the cells, which is antecedent to its being transformed into the active state, takes place slowly, it then acts as a formative force, and so may promote cellular growth; if, however, it occurs in too large a quantity, or continues for too long a time, it acts as a disintegrating force which endangers the structure of the cell, and therewith its vital activity.

The explanation I have here offered is, at all events, not a strained or improbable one, it is based on facts, and also explains the individual facts, and it may be allowed to stand until a better has been offered. If rachitis and osteomalacia should prove to be infectious diseases, as some pathologists suppose, then the question would arise whether the action of phosphorus in these disorders is not similar to that of quinine and arsenic in cases of malaria.

With regard to the special treatment of POISONING by phosphorus I have already said something, when lecturing on turpentine. I may mention in addition that the salts of copper[3] have been recommended for the purpose of neutralising the effect of phosphorus on the stomach. In this glass are a few cylindrical pieces of phosphorus covered with water. I drop into the water a small crystal of sulphate of copper, and gently shake the mixture. Very soon, especially if warmed, there is deposited on the phosphorus a black layer of phosphide of copper, which after a short time,

[1] Hugo Schulz, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxvii, S. 314; van den Corput, 'Pharmakol. Section des Internationalen Congr. in Berlin,' 1890.

[2] A. Gamgee, 'Journ. of Anat. and Physiol.,' 1877, vol. xi, p. 21.

[3] V. Bamberger, 'Würzb. med. Zeitschr.,' 1866, Bd. vii, S. 41.

—the phosphorus being oxidised by the oxygen in the cupric oxide—is converted into a red layer of metallic copper; the deposit becomes considerably larger on standing, until at last all the copper is deposited on the phosphorus. These small bits of phosphorus, thus coated over, emit the characteristic odour only when warmed, and are not luminous in the dark.

In cases of poisoning by the heads of lucifer matches or by phosphorus paste, which, being used for poisoning rats, is easily accessible, the copper salt acts still more quickly. The phosphorus being in a state of minute subdivision, a greyish-black mass is formed consisting chiefly of phosphide of copper, which is insoluble, and does not vaporise.

Von Bamberger recommends that an emetic of sulphate of copper should immediately be given in cases of poisoning by phosphorus. It seems to me, however, that it is unnecessary to administer this caustic substance in doses so large as to cause vomiting, but that it suffices if we administer several times about 0·25 gramme (about 4 grains) dissolved in a few tablespoonfuls of lukewarm rain-water, and then promote vomiting by tickling the fauces; this procedure should be repeated three or four times during the first half-hour. Ozonised oil of turpentine (see Vol. I, page 365) may now be administered in order to oxidise any portions of phosphorus which may be adherent to the lining of the stomach; after this vomiting should again be encouraged.

We must carefully avoid giving the patient milk, or anything which contains fat, since this dissolves phosphorus. As the poison is absorbed comparatively slowly from the intestine, the administration of some gentle aperient may be useful; castor oil, however, is inadmissible.

XIX.

Arsenic—Its action generally on the system—Liebig's explanation of its action—Theory of arrested decomposition of the body after death from arsenic—Transformation of either of the arsenical oxides into the other by living protoplasm—Similarity of action of the elements belonging to the tri- and quinque-valent group—The Styrian arsenic eaters—Increased nutrition, especially of the bones, induced by arsenic—Therapeutic uses—Treatment of cases of poisoning—Arseniietted hydrogen—Easy method of testing for arsenic.

ARSENIC is very closely allied to phosphorus, in its chemical, pharmacological, and therapeutic properties.

Some confusion has arisen with regard to its name. The term τὸ ἀρσενικὸν was applied by the Hippocratic School to one of the sulphides of arsenic, the golden-yellow trisulphide, As_2S_3, or native *Orpiment*, which they used as an external local application to indolent ulcers. They termed the disulphide, As_2S_2, which occurs native as *Realgar*, ἡ σανδαράκη, and employed it in the same way, as well as for other purposes,—among others, as a remedy in hysterical affections when mixed with wine, bitter almonds, and sulphur.

By roasting these two native minerals we obtain the white ARSENIOUS ACID, As_2O_3, the sulphur being dissipated and replaced by three atoms of oxygen, and it was to this compound that at a later date the Greek name was applied. ARSENIC, the name given to the metal, which was first obtained by Schröder in 1694 from arsenious acid, is a dense crystalline substance, of a steel-grey colour when fresh, but afterwards, from the formation of a suboxide, greyish-white and somewhat iridescent. Generally, however, when the term arsenic is used, the anhydrous arsenious acid, As_2O_3, or

one of its salts is the substance referred to. This also is the case in speaking of the effects of arsenic; but here we include the effects of two other soluble compounds, arsenic acid, As_2O_5, and its salts; and arsenietted hydrogen, AsH_3. Metallic arsenic, as such, is insoluble in the fluids of the body, but nevertheless, when administered internally, it is absorbed from the intestinal canal, probably in the form of arsenious acid; and it is also absorbed by the skin and cutaneous glands when, mixed with melted lanolin, it is injected subcutaneously or applied by inunction.[1] In this way it may produce the same therapeutic and poisonous effects as those which characterise arsenious acid.

Officinal arsenic, or arsenious acid, occurs as a heavy white powder or in sublimed masses presenting a stratified appearance, and when slowly sublimed in a glass tube it forms minute brilliant and transparent crystals of an octahedral or tetrahedral character. It is sparingly soluble in cold water. It crystallises out, in a regular form, from solutions in water, glycerine, or concentrated hydrochloric acid. Potash and soda readily combine with it to form the soluble salts, $KAsO_2$ and $NaAsO_2$.

Large doses, such as 0·05 to 0·15 gramme ($\frac{3}{4}$ to $2\frac{1}{4}$ grains), produce poisonous effects on human beings, violent INFLAMMATION OF THE STOMACH AND INTESTINES being the characteristic symptom; death results from paralysis of the heart and of the respiratory centre, consciousness is retained almost to the last. On post-mortem examination the glands of the digestive tract are seen to be inflamed; there is fatty degeneration of the muscular tissue of the heart, of the liver, and of the walls of the vessels; and resulting from the degeneration of the vascular walls, ecchymoses are produced in the most diverse organs, presenting very much the character of hæmorrhagic follicular ulcers. A considerable excess of urea is excreted,[2] and the amount of glycogen in the liver is diminished.[3] The inflammation

[1] Schroff, 'Zeitschr. d. Ges. d. Aerzte,' Wien, 1859, No. 29; Paschkis u. Obermeyer, 'Med. Jahrbücher,' Wien, 1888, S. 117.

[2] Gaehtgens und Kossel, 'Centralbl. f. d. med. Wissensch.,' 1875, S. 529, und 1876, S. 831.

[3] Saikowsky, 'Centralb. f. d. med. Wissensch.,' 1865, S. 769, 'Arch.

of the stomach and intestines presents the characters of adenitis parenchymatosa,[1] similar to that produced by phosphorus. In rapidly fatal cases gastro-enteritis may be entirely absent, and death take place simply from paralysis of the nervous centres.

We must here note particularly that the gastro-enteritis is produced essentially through the agency of the circulation. If arsenious acid or one of its salts is injected subcutaneously in the back of an animal, no corrosive action is perceptible at the puncture. On the other hand, unless the poison produces rapidly fatal paralysis, we find after a few hours violent inflammation of the stomach and the whole of the small intestine. A cold saturated solution of arsenious acid or of arseniate or arsenite of sodium (1 in 20), injected into the conjunctival sac of a rabbit, causes there only a slight redness. In any case arsenic when brought in contact externally with living tissue acts as a caustic only after a considerable interval, and it produces its effects on distant parts only after it has been in some way or other absorbed into the system. It possesses no recognisable direct affinity for albumen, and, in the words of a distinguished German investigator,[2] "it is probably only in the organism that it is transformed into a poisonous compound. . . . We are at present unable to indicate with any degree of probability the nature of the combination by which the effects of arsenic are produced."

Liebig thought at one time that he had solved the problem. He imagined that arsenious acid, like corrosive sublimate, possessed the power of forming with albumen a stable, non-putrefactive compound. He considered that this took place also in the living tissue, and by preventing the normal changes of the living albumen brought about its death.[3] Liebig, however, nowhere demonstrates the

für pathol. Anat.,' 1865, Bd. xxxiv, S. 73; Naunyn, 'Handb. d. spec. Path. u. Therapie,' 1876, Bd. xv, S. 351; Heffter, 'Arch. f. exper. Path. u. Pharmak.,' 1890, Bd. xxviii, S. 97.

[1] Virchow, 'Arch. f. pathol. Anat.,' 1869, Bd. xlvii, S. 525.

[2] Buchheim, 'Lehrbuch der Arzneimittellehre,' 1878, S. 309.

[3] Liebig, 'Die Chemie in ihrer Anwendung auf Agricultur und Physiologie,' 1843, S. 463.

production of this arsenical albuminate, and he himself abandoned the theory. It has never been accepted by biologists, but is still occasionally advanced by some chemists. Apparently they are unacquainted with the experiments undertaken by Herapath in 1851, in order to produce Liebig's hypothetical arsenical albuminate.[1] Herapath conclusively proved that no such compound exists.

It can very easily be shown that the action of corrosive sublimate has little in common with that of arsenic, as regards the point at present under our consideration. Sodium arsenite produces no change in a clear watery solution of albumen; a cold saturated solution of free arsenious acid produces a slight precipitate, which, however, is less than that from free carbonic acid; a feebly alkaline solution of sodium arseniate produces likewise no effect upon a clear solution of albumen; whilst free arsenic acid, like other mineral acids, produces a copious deposit.

Nor can the ANTISEPTIC property of arsenic be rightly compared with that of corrosive sublimate, the difference in the activity of the two being very marked. It has been often asserted that the corpses of those who have died from the effects of arsenic do not undergo decomposition, but this is a tradition which exists only in text-books and in various judicial records. It is quite true that where large quantities of arsenic have been in contact with the viscera, decomposition is thereby retarded; but in cases where poisoning has resulted from a moderate dose, and where this has been absorbed and distributed in the organism, decomposition takes place in the usual way. This has been known for a long time and proved repeatedly,[2] but the legend as to the mummification of individuals poisoned by arsenic has held its ground up to a very recent period. It is to be hoped that the latest and most exhaustive investigation[3] of the matter has finally exploded this error.

[1] Herapath, 'Philosophical Magazine,' 1851, p. 345.

[2] Orfila, 'Vorlesungen über gerichtliche Arzneikunde,' 1822, S. 88; ibid, 'Lehrbuch der Toxikologie,' 1852, i, Ss. 372—377; Wöhler, 'Die Mineralanalysen in Beispielen,' Göttingen, 1863, Ss. 230—231.

[3] T. Zaaijer, "Das Verhalten der Leichen nach Arsenikvergiftung," 'Vierteljahrschrift f. gerichtl. Med.,' 1886, Bd. xliv, S. 249.

No other explanation, so far as I am aware, of the poisonous action of arsenic has hitherto been advanced. Possibly the results of some experiments made by Hugo Schulz and myself may throw some light on the subject; they undoubtedly furnish an explanation of most of the facts gained by experience and research.

We started with the assumption that arsenic, which behaves both as a triad and as a pentad element, could act as a carrier and as a discharger of loosely combined oxygen, just in the same way as the triad and pentad nitrogen; arsenious acid corresponding with NO, and arsenic acid with NO_2. When the nitrogen in the animal tissues discharges or combines with oxygen, the tissue undergoes considerable destructive change. Are these same tissues also capable of developing in arsenic this varying absorption and discharge of oxygen? The well-known facts that arsenious acid is a powerful reducing agent, and that arsenic acid is a still more powerful oxidising agent, lent a certain probability to the answer being in the affirmative.

It would occupy us too long if I entered into all the details of the experiments[1] which were made on different parts of the animal body. I will merely state that the tissues were recent, and when necessary were cut into small pieces; they were then placed in neutral solutions of sodium ARSENITE and ARSENIATE, and digested at blood-heat. The subsequent chemical examination invariably showed that in the presence of living PROTOPLASM arsenious acid was oxidised into arsenic acid, and that the latter was also reduced to arsenious acid, and consequently that both oxides were always present when one of them had been used in the experiments.

Blood had extremely little oxidising power on arsenious acid, but acted in a strongly marked manner as a reducing agent on arsenic acid.

The mucous membrane of the stomach, the pancreas, and the brain have an oxidising power on arsenious acid, the power of these tissues increasing in the order given; they have also

[1] C. Binz u. H. Schulz, 'Arch. f. exper. pathol. und Pharmak.,' 1879, Bd. xi, S. 200; 1881, Bd. xiii, S. 256; Bd. xiv, S. 345; 1882, Bd. xv, S. 322; 1895, Bd. xxxvi, S. 275.

a reducing power on arsenic acid, the activity of the tissues being in the reverse order. This reverse order may arise from the As_2O_3 which results from the reduction of the As_2O_5 constantly undergoing re-oxidation. The same effects are produced by the liver, which appears to possess the highest oxidising power of all the viscera with which we experimented.

It is only by LIVING protoplasm that arsenious acid undergoes oxidation; when thoroughly boiled—that is to say, when dead—protoplasm has no such action.

Following upon these experiments, which were made with organic tissue in a dying state, we had still to prove that changes similar to those above described took place when the two arsenical oxides were brought in contact with the LIVING tissues of LIVING animals. The proof that it was possible for the arsenical oxides to undergo oxidation and reduction was established in the following manner:

A rabbit or a dog, after being kept for a day without food, was rendered insensible by means of ether. A coil of intestine about 20 cm. long was drawn through an incision in the middle line of the abdomen, and tied at both ends. From 8 to 10 c.c. of a solution of sodium arseniate (prepared by making a cold, nearly saturated solution, and then gently warming it), or of a saturated solution at 40° C. (104° F.) of the crystalline arsenious acid, was injected into this coil by means of a Pravaz syringe. The coil of intestine was then returned, the wound of the abdomen sewn up, and the animal placed in a room having a temperature of about 29° C. (84·2° F.). After the lapse of half an hour the animal was killed, the coil of intestine was recovered and separated, and its contents placed in a dialyser together with some water in which a small quantity of alkali had been dissolved.

After each experiment it was found, by careful chemical analysis, that both oxides of arsenic were present in the intestines, though only one of the oxides had been injected.

So far we have arrived at the following facts:

1. In the animal organism arsenious is converted into arsenic acid, and arsenic acid is likewise converted into arsenious acid.

2. These two transformations are rapidly produced both within the body and outside it by means of protoplasmic tissue.

3. The experiments performed outside the body demonstrate that the viscera which are more particularly affected by arsenic during life, are precisely those by which arsenious acid is readily oxidised.

Arsenic, therefore, must be regarded merely as the carrier of oxygen, the latter being the active agent. This hypothesis, which undoubtedly is opposed to the theories previously advanced as to the action of arsenic, has nothing out of the way or unusual about it. The results of our experiments justify us in saying that there is no reason against assuming that arsenic may probably possess certain qualities, the existence of which has been demonstrated in the case of nitrogen.

NO, oxide of nitrogen, nitric oxide, acts as a caustic on animal tissues; combining with oxygen it is converted into the red fumes of the strongly oxidising agent, NO_2, nitric peroxide, or hyponitric acid.

NO_2 destroys the tissues, as it is decomposed by water and reconverted, in part at least, into NO.

Nitrogen itself takes no direct part in these changes; it is simply and solely the carrier and distributor of the energetic atoms of oxygen.

The destructive changes which are brought about by oxygen can be clearly demonstrated by another example which is of daily occurrence. Ferric oxide continuously furnishes to organic tissues an atom of oxygen, and is reduced to the form of ferrous oxide. This, however, cannot exist in the presence of air or water, and is almost instantaneously reconverted into ferric oxide. The organic tissues are wasted or consumed by this continuous interchange of oxygen. The timbers of a ship at the spots through which nails have been driven present a half-charred appearance. Spots of rust on linen cause it to rot and fall into holes.[1] Organic substances in the soil are decomposed under the action of ferric oxide. The ferrous oxide lying in the deeper layers of the soil is turned up by the plough,

[1] Graham-Otto, 'Lehrbuch,' 1872, Bd. ii, S. 1052.

and being converted into ferric oxide produces the result above mentioned.[1]

The following table enables us to compare the changes which nitrogen, iron, and arsenic respectively undergo, in accordance with the properties described above:

NO	becomes	NO_2,	and is reconverted	into	NO.
$2FeO$	,,	Fe_2O_3	,,	,,	$2FeO$.
As_2O_3	,,	As_2O_5	,,	,,	As_2O_3.

These several processes differ in regard to each element only by the rapidity with which they take place. With nitrogen the change occurs very quickly, with iron slowly; arsenic occupies an intermediate position. If an ointment or paste containing arsenious acid is applied externally to parts from which the epidermis has been removed, some hours always elapse before any burning sensation is felt; nitric oxide produces this effect instantaneously.

We must not omit to mention here the difference in the mode of action of the two oxides of nitrogen and of arsenic: the former produce their destructive effects on the parts to which they are applied; the latter only within the tissues.

This difference is of no importance so far as we are concerned, as it does not affect the argument, and it has no real existence. We are, in fact, able to develop the corrosive oxides of nitrogen within the tissues, and we then see how completely the effects resemble those of the arsenical oxides. On this point I would refer you to what I have previously said when discussing the effects of sodium nitrite.

By further investigations, Hugo Schulz and I have confirmed and extended our theory that oxygen is the prime factor by which the effects of arsenic are produced.

In the first paper which we published on the subject we called attention to the fact that the action of the arsenites on the alkaline mucous membrane of the intestines was STRONGER than that of the arseniates. We thereby confirmed the statements of previous authors, who maintained that, given the same amount of metallic arsenic, the arsenites were more rapidly poisonous and produced death more quickly in healthy animals than the arseniates. The nature

[1] Liebig, loc. cit., 1876, 9 Aufl., S. 100.

of the effects produced is, as is well known, precisely the same; it is with regard to the rapidity of their action that they differ.

When arsenious acid is introduced into the circulation, and thereby passes to the glandular organs in the abdomen or to the central nervous system, it rapidly deoxidises or reduces the protoplasm of these organs, and is itself converted into arsenic acid. The latter is in the capillaries and veins very readily again reduced to arsenious acid, and is then capable of repeating its action on the protoplasm as often as it is carried to the latter. The process thus goes on continuously so long as the arsenic remains in the system.

I may also mention here that such organs as the liver and kidneys, which are more particularly sensitive to the action of arsenic, and which rapidly undergo change in consequence—a point which I myself have demonstrated as regards the liver,—absorb and retain a larger quantity of the drug than those which are less sensitive to its effects.[1] This is a further proof of the close affinity which exists between certain cells and arsenic.

Between arsenic and BLOOD no natural affinity exists, and no change results from their admixture. If in the living body the blood appears somewhat changed after the administration of poisonous doses, this is due to the changes which have previously been produced in the respiratory centre. A frog, the blood of which had been replaced after the usual method by a saline solution, and which jumped about vigorously, succumbed to the effects of arsenic in precisely the same way as a normal animal.[2]

The CIRCULATORY SYSTEM is affected by the action of arsenic. The capillary walls undergo extensive degeneration, leading to hæmorrhage and ulceration, and the heart is paralysed. The arteries, especially those of the abdomen, may be either contracted (Lesser) or dilated and paralysed (Böhm), according to the poisonous stage. The paralysis of the vessels, however, is in no way connected with the

[1] E. Ludwig, "Die Verteilung des Arsens im tierischen Organismus," 'Medicin. Jahrbücher, Wien,' 1880.

[2] Lewisson, 'Archiv f. Anat. u. Physiol.,' 1870, S. 352.

fatty degeneration of the capillaries, the epithelium, or the glands; nor with the ulceration of the follicles, nor the general wasting, nor the exudations of false membranes resulting from variously transformed cells; nor, in short, with any of the destructive changes in the stomach and intestines which are characteristic of the results of arsenical poisoning. At any rate, such changes have never as yet been developed elsewhere, in a few hours, from simple vascular paralysis. That the paralysis of the vessels helps to lower the blood-pressure beyond that which results from the enfeebled action of the heart, is self-evident. Under certain conditions it may certainly accelerate the fatal termination; it is nevertheless always of secondary importance.

I then proceeded to test the effects of arsenic by experiments similar to those which I described when referring to phosphorus. These experiments confirmed the conclusions drawn from other facts, namely, that arsenic only acts as a caustic when in contact with GLANDULAR TISSUES, whereas connective tissue is almost unaffected by it.

The similarity in the chemical and toxicological behaviour of the group of tri- and quinque-valent elements is very remarkable. This group consists of nitrogen, arsenic, phosphorus, antimony, bismuth, and vanadium.

NITRIC OXIDE, NO, is a strongly reducing agent; nitric peroxide, NO_2, is a powerful oxidiser. It is these properties that unquestionably render them so destructive to tissue. The nitrogen takes no direct part in the process; this is entirely dependent upon the combined oxygen, which constantly varies in amount, becoming nascent, active, atomic, or whatever other name you like to give it.

PHOSPHORUS behaves in a similar manner. The effects produced on the tissues and the symptoms associated with phosphorus poisoning (paralysis, fatty degeneration of the cells, increased secretion of urea, &c.) correspond with those produced by arsenic even in slight details. Owing to the more rapid action of phosphorus when given in the same dose as arsenic, the effects on the nervous system preponderate over those on the alimentary canal, and the narcosis is more profound. The effects of phosphorus, in

consequence of its strong affinity for oxygen, are rapid and distinct, unless administered in a very diluted form. The same dose of arsenic requires more time to produce its effects, as its affinity for oxygen is not so strong. This is the reason why the dose which in the case of arsenic produces no poisonous effect will, in the case of phosphorus, lead to dangerous results.

ANTIMONY, when administered in a soluble form, acts as a poison, the effects of which are, as has been correctly stated, almost precisely analogous to those produced by arsenic. In no single feature is there any essential difference, and the disintegrating action on organic tissues is not due, as in the case with other metallic poisons, to its actual deposit and presence in those tissues. I will give you a few illustrations. An ointment containing antimony (Unguentum Antimonii Tartarizatum), when rubbed into the skin, acts in the same way as one containing arsenic, and produces after a time similar results. Albumen is not precipitated by the neutral salts of antimony, and yet these act as irritants or caustics. As was already known to Orfila and Magendie, tartar emetic applied externally will set up inflammation of internal organs. Saikowski has recorded instances of fatty degeneration of the glandular tissues and the muscular tissue of the heart in animals as the result of giving them antimony along with their food, the effects resembling those produced by the administration of phosphorus.

We know from the results of chemical investigation that the trioxide of antimony, Sb_2O_3, is also a powerful reducing agent, but when heated to redness it absorbs oxygen and is converted into the tetroxide, Sb_2O_4. The latter compound is, on the other hand, also produced by heating the higher oxide, the anhydrous pentoxide, Sb_2O_5, to redness. Sb_2O_4 is therefore intermediate to the other two oxides, and one of the characteristic properties of antimony is that, precisely like arsenic, atoms of oxygen can either be absorbed or given off by it. The expenditure of energy, and the rapidity and facility with which the effects are produced, are less marked than with nitrogen, phosphorus, and arsenic, and consequently the poisonous effects are proportionally less.

Experiments on animals with the soluble salts of BISMUTH have produced similar results,[1] and the metal possesses similar chemical characteristics to those of arsenic and antimony.

Certain experimental investigations[2] on the action of VANADIUM seem to indicate that it acts in a similar fashion. Experiments were made on several species of animals with sodium orthovanadate (Na_3VO_4), and its similarity of action to that of the substances above described was shown in the following particulars. Vanadic acid has a slightly antiseptic action. It paralyses the cardiac, respiratory, and motor centres, and produces unconsciousness. It sets up inflammation of the alimentary canal, by whatever part of the body it is introduced. The lower oxides of vanadium are readily converted into the higher, at the expense of contiguous molecules containing oxygen, whilst the higher oxides just as readily part with their oxygen in the presence of substances having a reducing power.

It is evident, therefore, that, regarded from the above point of view, the very varied and apparently diverse toxicological effects of the six members of the nitrogen group really result from the same cause. As regards the oxides of nitrogen, this cause undoubtedly is the great activity of the oxygen atoms; with regard to the other substances—and most distinctly in the case of arsenic—we may, from the uniform results of our numerous experiments and the inductions therefrom, at least assume that the effects are produced by the same or a similar cause.[3]

[1] L. Feder-Meyer, 'Rossbach's Pharmakol. Untersuch.,' 1882, Bd. iii, S. 235.

[2] A. Gamgee and T. Priestley, 'Philosoph. Trans. Roy. Soc.,' 1876, vol. clxvi, pp. 495—556.

[3] The objections raised by Dogiel and Filehne in opposition to these views, as based on chemical errors and false conclusions, are fully discussed in my third paper in the 'Arch. f. exper. Path. u. Pharmakol.,' 1881, Bd. xiv, S. 345.

We may now pass on to consider one action of arsenic which has a special bearing on its therapeutic application. I refer to the increased DEVELOPMENT OF THE ANIMAL TISSUES which results from its cautious use.

In those countries where arsenic occurs native, as a mineral in the form of sulphides, and is consequently easily obtained, it seems to have been known from an early period that horses looked better and displayed greater activity if arsenic was added—in carefully adjusted quantities—to their food. The people themselves also took it, and consequently in these districts habitual arsenic eaters are to be found, who systematically use the poison for the same purpose. Certain accounts from Styria were published,[1] and were received with some incredulity at first; in 1857, however, arsenic was found in the urine of a workman in that district.[2] The Government authorities then requested the Styrian doctors to furnish accurate reports on the matter, and the above-mentioned statements were entirely corroborated.

The arsenic eaters are met with chiefly in the north and north-west of Styria: arsenious acid is the favourite form of the drug, but the yellow insoluble orpiment is also used; this always contains the acid, and is partly converted into it in the intestine. A dose the size of a millet seed (about ½ grain) is taken when the moon is in its first quarter; this is increased gradually to the size of a pea or even more during full moon; the dose is then gradually diminished, and altogether discontinued during the new moon. Some arsenic eaters abstain from liquids directly after the dose, others avoid fatty food; the greater number, however, make no change in their mode of living, and are accustomed to take alcoholic liquors with the dose. These people, who are mostly woodcutters, stablemen, smugglers, and foresters, are, as a rule, strong and healthy, and it is a desire to maintain their health that leads

[1] Schallgruber, 'Med. Jahrb. d. österr. Staates. Graz,' 1822, Bd. i, S. 99; v. Tschudi, 'Wiener med. Wochenschr.,' 1851, S. 453, und 1853, S. 4.

[2] E. Schäfer, 'Sitzungsber. d. Akad. Wien,' Bd. xxv, S. 489 (Math.-physik. Classe), und 1860, Bd. xli, S. 573.

to the habit of arsenic eating. Individuals who are accustomed to its use experience a sensation of warmth in the stomach soon after taking it; they can tolerate large doses without vomiting, and it is only after immoderate doses that any feeling of dizziness is induced. Such a condition of things may continue for twenty or thirty years; smaller doses than usual, or their temporary discontinuance are followed by general weakness, which obliges the sufferer to resume his former habit. Arsenic eaters are sometimes, though rarely, found amongst women.

"Although the perfect health developed by the hardy surroundings of our Alpine population may counteract the baneful effects of arsenic, and although the system is slowly prepared by commencing with small doses and gradually increasing them until it is habituated to large doses, yet many arsenic eaters fall into chronic weakness notwithstanding their perfect constitution." Such, without further comment, is the statement of the official reporter.[1] Many individuals began the habit at eighteen years of age, and nevertheless lived to the age of seventy-six.

Arsenic eaters generally conceal this habit or infirmity. Dr. Knapp, of Obergeiring, however, has published some accounts which were communicated to him. The following is from his official report:—"J. W.—, a woodcutter, aged thirty years, strong and active, and always enjoying good health, had taken arsenic for the last twelve years. He began with minute fragments, but afterwards took larger pieces twice a week. For a few weeks at first he experienced a great feeling of weakness, but this always passed off on renewing the dose. He never felt any burning sensation either in the throat or stomach. Only once, after taking a piece the size of a horse-bean, in order to dissipate the effects of excessive drinking, had he experienced any stupor or cerebral discomfort. On the 22nd of February, having already on the previous day, as he stated, swallowed his usual

[1] E. Schäfer, in his capacity of Government analyst at Gratz, investigated in two years twenty cases of poisoning, of which thirteen were due to arsenic. He does not state, however, how many of the deaths occurred in arsenic eaters, nor how many were due to the *arsenic being* criminally or accidentally administered.

portion, he took a piece weighing 0·27 gramme (4 grains) in Dr. Knapp's presence, crushed it with his teeth, and swallowed it. On the 23rd he did the same with a piece weighing 0·33 gramme (5 grains). During these days he eat and drank with his usual appetite, and went home on the 25th of February perfectly well. His urine was examined on the 22nd by E. Schäfer, and gave the usual arsenical deposit with Marsh's test."

At the congress of German physicians and naturalists held at Graz in 1875 Dr. Knapp brought before the medical section two Styrian arsenic eaters, one of whom, in the presence of the members, swallowed 0·3 gramme (4½ grains) of orpiment; the other a workman, twenty-five years of age, took 0·4 gramme (6 grains) of arsenious acid.[1] One of these men, who was in the habit of taking a little arsenic once a week with his bread or bacon, was always in good health and spirits, but if he went without his usual dose he had a certain feeling of discomfort until the dose was repeated. On the following day the two men appeared again before the meeting in perfect health, and two days later the arsenical deposit obtained from their urine by Marsh's test was shown to the meeting.

Knapp expressly stated on this occasion that no case of arsenical cachexia among habitual arsenic eaters had ever come under his observation; he had, however, seen an instance of acute poisoning from the drug in a man who, whilst intoxicated, took too large a dose—a piece the size of a bean; the man completely recovered, and cautiously resumed his previous habit.

For the present it is impossible to explain how the system becomes accustomed to strong poisons, though the fact is daily observed with regard to nicotine and morphine. A conceivable explanation may be furnished by the changes in the amount of oxygen in the cellular protoplasm which are induced by the action of arsenic; we can at least imagine that the organism gradually adapts itself to the increased activity of an element—namely, oxygen—for which

[1] Knapp, 'Tageblatt der 48, Versammlung.,' Ss. 68, 107, und 219; 'Ergänzungsheft zum Centralbl. f. öffentl. Gesundheitspflege,' Bonn, 1885, ii, S. 1.

it has a close affinity. A stimulus, if frequently repeated, must be exhibited in increasing doses in order each time to produce a certain effect; and this is more easily accomplished if the stimulus is not extraneous, but is simply the methodically increased action of a substance which is everywhere, to a certain extent, present in the system.

The details with regard to the action of arsenic have been further investigated by experiments on animals. As far back as 1863 it was reported[1] that two young rabbits, to each of which 0·1 gramme (1½ grains) was daily given in its food, became very lively after they had been gradually accustomed to the dose, and grew to an extraordinary size.

Numerous experiments were made by Giess[2] on rabbits, fowls, and young pigs; he obtained most surprising results, as you can see from the photographs which I here place before you. The bones of those animals to which arsenic was administered can be distinguished at a glance from those of the control animals. The offspring of a mother to whom arsenic had been given all died at birth, apparently because they were too large,—at least there was no other manifest cause. Consequently in this case also, the arsenious acid acted as a stimulus to the development of tissues. The condition of the individual bones was essentially the same as that produced by Wegner from the administration of phosphorus. More recent observations[3] furnish results closely agreeing with the above, and lead to the following conclusions:

Small doses of arsenic cause proliferation of the cells of the liver and kidneys. In animals small doses of phosphorus act on the liver precisely in the same way as arsenic,—that is to say, they stimulate the growth of the various cells; larger doses give rise to fatty and vacuolar degeneration, and to necrosis and destruction of the liver cells. Neither the blood nor the vascular system is affected.

Phosphorus and arsenic, moreover, do not induce these morbid changes by acting to any extent on the structures

[1] Roussin, 'Journ. de Pharmacie et de Chemie,' 1863, S. 121.

[2] Th. Giess, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. viii, S. 175.

[3] E. Ziegler und Obolensky, "Experimentelle Untersuchungen über die Wirkung des Arseniks und des Phosphors auf die Leber und die Nieren," in Ziegler's 'Beiträgen,' Jena, 1888, Bd. ii, S. 291.

surrounding the cells,—that is to say, by lessening any external resistance to the development of the cells, but by acting chiefly on the cells themselves. At the same time mitotic or indirect division of the nuclei is distinctly manifest.

In discussing the THERAPEUTIC USE of arsenic I must limit myself to enumerating the conditions in which it is more particularly of service. It is now employed in so many diseases, that a full explanation of its effects can only be given by a series of clinical lectures.

Arsenic was so frequently used for criminal purposes that it was brought into disrepute as an internal remedy, and was regarded with much the same distrust as phosphorus has been in our times, in consequence of its frequent employment with murderous or suicidal intent. From the time that *Acqua di Tofa,* which is essentially an arsenical solution, was discovered in Italy in the fifteenth century, up to the time when it became known how easily the presence of the mineral could be detected in the dead body, and also till legal restrictions were placed upon its sale in the present century, arsenic was the agent most generally employed both by low-born and aristocratic murderers.[1]

In 1619 a paper was published in Rome, recommending the employment of arsenic as a remedy,—P. Castelli, Dubitationes in usu Olei Vitrioli et defensio antiquorum in Arsenici atque Sandarachæ potu." A hundred years later the degree of doctor of medicine was conferred by the University of Jena on J. H. Slevogt in recognition of his 'Invitatio ad inauguralem dissertationem de Arsenico, cui modesta eius excusatio præmittitur.' In 1786 T. Fowler's 'Medical Reports on the Effects of Arsenic in Cases of Agues, Remittent Fevers, and Periodical Headaches' was published. In 1811[2] E. L. Heim recommended the employment of arsenic, but in the following year K. L. Donner, with the approval of Hufeland, published a work, 'Abhandlungen über die höchst verderblichen Folgen des innern Gebrauches

[1] "Le poison est le vrai fléaux des princes"—so writes F. G. de Pitaval, 'Causes célèbres,' Paris, 1738, vol. i, p. 467.

[2] See also C. F. Harles, 'Ueber die Heilsamkeit des Arseniks gegen Wechselfieber,' Frankfurt, 1810.

des Arseniks in Wechselfieber' (Reports upon the highly injurious effects of the internal administration of arsenic in intermittent fever).

At the present day arsenic is given by the mouth or injected subcutaneously or into the viscera in the most diverse forms of disease,—such, for instance, as all forms of neuroses, malarial fever, malignant lymphoma, and cutaneous disorders. In the German Pharmacopœia the maximum single dose, of course under ordinary conditions, is stated to be 0·005 gramme (about $\frac{1}{12}$ of a grain), and the largest amount to be given in a day 0·02 gramme ($\frac{1}{3}$ of a grain); and by fixing the doses at these amounts the danger of administering the remedy in a reckless or careless manner is indicated. In actual practice, however, much larger quantities are given, as appears from the following quotation from Hebra's work:[1] "In obstinate cases of psoriasis I have gradually increased the number of pills given daily to twelve, that is the quantity of arsenic taken daily was $\frac{9}{10}$ of a grain, and patients have taken this quantity without intermission for several months. Many patients consequently, before being freed from their cutaneous disorders, have taken as many as two thousand pills, or upwards of 160 grains of arsenious acid. The patients, of course, whilst taking such large doses were always under medical supervision, and their symptoms were carefully watched. In no instance were any unfavorable effects produced by the arsenic, and therefore in the treatment of obstinate cutaneous affections of that character we can without any hesitation recommend that the remedy should be employed in equally large doses."

The composition of the pills above referred to is—

Acid. Arsenios. 0·5 (grana viiss).
Piper. Nigr. 5·0 (grana lxxv).
M. Ft. pilul. No. 100. Consp. pulv. Cinnamomi.
D. S. One pill to be taken night and morning.

It is advisable, when giving this remedy for the first time to a patient, to prescribe only half the above quantity, that

[1] Hebra, 'Handb. d. spec. Path. u. Therapie,' Erlangen, 1862, Bd. iii, S. 294.

is 0·25 gramme ($3\frac{3}{4}$ grains) in 100 pills, and then gradually to increase the dose if no injurious effects are produced. The first indications of the latter are disturbances of the digestive function, vomiting after food, and tenderness of the stomach on pressure—symptoms closely resembling those of gastric ulcer. If the remedy be not discontinued these symptoms are followed by loss of flesh, inflammation and catarrh of the external mucous membranes, diarrhœa, disordered sensation and movements, a further increase in the gastritis, dropsical swellings, hectic fever, and great prostration.

Following on the exhibition by Knapp of the two arsenic eaters at the meeting previously referred to, Kaposi reported that one of his patients suffering from a chronic skin disease (lichen rubrum) took within twelve months as much as 22·5 grammes (about 340 grains) of arsenic, the result being very satisfactory, and no poisonous symptoms being developed.

The use of arsenical mineral waters has recently been introduced; among them I may mention that of Roncegno, in South Tyrol, a few miles east of Trent. This water contains 0·1 gramme ($1\frac{1}{2}$ grains) of arsenic[1] to the litre (35 ounces), together with a large amount of ferric oxide, which gives it a brown turbid appearance. It is obvious that the combination of arsenic with iron necessarily limits the absorption of the former by the intestinal canal. Baden Baden, which contains 0·264 mg. (about $\frac{1}{250}$ of a grain) to the litre, ranks first amongst German mineral waters.[2]

The ætiology and pathology of most of the diseases in which arsenic improves or cures, are somewhat obscure. I will merely refer to the various forms of neurosis in which it is employed. Sometimes, in long-protracted cases of nervous or other disorders, arsenic may produce such an improvement of the general nutrition that the body is able to withstand the noxious influences acting upon it, and to overcome the morbid changes resulting therefrom. It would be wrong, however, to draw general conclusions from isolated instances. If, in a case of malignant lymphoma, a rapid

[1] C. Binz, 'Berl. klin. Wochenschr.,' 1892, No. 15.

[2] Frey, 'Deutsche med. Wochenschr.,' 1886, S. 306.

absorption of the protoplasmic cells of which the tumour consists, is observed to take place after injections of a solution of potassium arseniate; or if, after the administration of arsenic for a few days, a cure occurs in a case of malarial disorder which had previously resisted the action of quinine; or if, in a case of recurrent fever[1] treated with arsenic, the temperature rapidly falls, the spirilla either decrease in number or become motionless, and the paroxysms subside, we can hardly attribute the effect to a mere improvement in the general condition of the body, or to its power of resistance to the micro-organisms being miraculously intensified. Nor can we assume that the normal cells are stimulated by the action of arsenic, any more than they are in the treatment of syphilis by mercury, or in the treatment of gummata by potassium iodide, of malarial infection by quinine, or of acute rheumatism by salicylic acid.

Still more conclusive against any such speculative theory as to the activity of the cells being stimulated or intensified, are the absolute facts themselves.

In cases of malignant lymphoma[2] treated at the Jewish Hospital in Berlin by the internal administration of arsenic, the following effects, among others, were noted:—" A decline in the severity of the morbid symptoms was not always coincident with improvement in the general condition of the patient. Although the patients felt much easier there was no improvement in their cachectic condition; sometimes, in fact, it was much more marked. They presented a pitiable appearance, with their pallid, greyish-yellow complexions and wrinkled skins. It was only after the course of treatment was completed, and they had discontinued taking the arsenic, that they seemed to improve in health and increased in weight. This general improvement in the appearance of the patients, moreover, was not materially modified by subsequent relapses, provided the treatment after the relapse was not deferred for too long a time."

For these reasons, and on the ground that the action of arsenic paralyses cells in general, and leads to their fatty

[1] Bogomolow, Wratsch, 1883; ref. 'Centralbl. f. klin. Med.,' 1883, S. 842.

[2] Karewski, 'Berliner klin. Wochenschr.,' 1884, S. 276.

degeneration and disintegration, the following view of the matter seems to me to be the most probable one. The cure of certain diseases accompanied by parasitic or hyperplastic cell-growth results from the direct effect of arsenic upon the morbific agent, which is much more sensitive to the action of the remedy than are the normal cells of the body. If only a slight diminution in the virulency of the morbific agent be produced, the normal cells are enabled to resist its action and destroy it.

In your clinical work you will be able to test the truth of this view. I will here only refer to one more experimental result bearing upon the question, namely, the proof which exists of the extreme sensitiveness of certain parasitic organisms, which act as morbific agents, to the action of arsenic.

R. Koch tested the restraining influence of several antiseptic agents, on the growth in a favorable medium of the anthrax bacilli. He found that a solution of corrosive sublimate of a strength of 1 in 1,000,000, or a solution of 1 in 330,000 of the ethereal oil of mustard, or of 1 in 100,000 of potassium arsenite, distinctly checked the growth of these micro-organisms.

Other well-known antiseptics, such as carbolic acid, salicylic acid, boric acid, and camphor, which are less active, came next in order.[1]

Some of the lowest organisms thrive, as has long been known, in solutions of arsenic.

It follows from this that little importance is to be attached to the statement, when made without any limitations, that arsenic only possesses feeble antiseptic properties. Its action in this respect can only be judged with reference to its effect on each single species when cultivated in some particular medium.

A remedy such as arsenic, which can be employed in so many and such different morbid conditions of the organism, will naturally produce various undesirable collateral effects according to the idiosyncrasies of different individuals, and in particular cases these effects will be very readily

[1] R. Koch, in 'Mitteil. a. d. Kaiserl. Gesundheitsamte,' 1881, Bd. i, S. 271.

induced. In prescribing it, therefore, these contingencies, which may take the form of cutaneous affections,[1] or sudden disturbances of the digestive tract, must be taken into account. Extensive brown discoloration of the skin, more especially affecting the face, has been observed;[2] the colouring matter in recent and slight cases was deposited in granules in the lymphatic spaces of the papillæ; in more chronic and severe cases in the lymphatic spaces of the cutis vera: it appeared to be altered blood-pigment, and slowly disappeared on the arsenic being discontinued. Among the cutaneous eruptions herpes zoster may be specially mentioned.[3]

LIQUOR KALI ARSENICOSI, Liquor Arsenicalis, Fowler's solution, is a strongly alkaline liquid containing 1 per cent. of arsenious acid, which is prepared by mixing together arsenious acid and potassium carbonate; the soluble metarsenite $KAsO_2$ is thereby formed, the excess of potassium carbonate remaining in solution. SPIRITUS LAVANDULÆ is also a constituent. This serves a double purpose: in the first place, its aromatic odour gives a distinctive character to the clear watery solution; and secondly, it prevents the formation of hyphomycetes, which otherwise are readily developed in a solution of potassium arsenite. The maximum dose is 0·5 gramme (8 minims) the largest amount to be given in a day is 2 grammes (30 minims).

Subcutaneous injections of Fowler's solution cause considerable pain on account of its alkaline reaction; this may be prevented by previous neutralisation with some innocuous acid, such as acetic acid.

Spiritus Lavandulæ, above mentioned, is a spirituous infusion of the fragrant flowers of the *Lavandula officinalis*. Formerly infusions of other substances of a similar nature were employed for the same purpose,—such, for instance, as Spiritus Melissæ, spirit of balm. It was found, however,

[1] Escherich, in Gerhardt's 'Mitteil. d. med. Klinik zu Würzburg,' 1886, ii, S. 337.

[2] G. Kirchgässer, 'Vierteljahrschr. f. gerichtl. Med.,' 1888, Bd. ix, S. 103; O. Wyss, ref. 'Centralbl. f. d. med. Wiss.,' 1891, S. 42; R. Förster, 'Berl. klin. Wochenschr.,' 1890, S. 1150; 1892, S. 262.

[3] L. Nielsen, 'Monatsh. f. prakt. Dermatolog.,' 1890, Bd. xi, No. 7.

that with these the arsenical solution soon became turbid—an effect which does not take place when spirit of lavender alone is added.

Chronic arsenical poisoning is treated simply by removing the cause from which it arises; cases of acute poisoning are treated by administering some substance which will combine chemically with the arsenic in the stomach, and by relieving the conditions resulting from the absorption and circulation of the poison in the system.

Bunsen [1] recommended recently precipitated ferric hydrate as an antidote, and it is the one most generally administered in cases of arsenical poisoning. Ferric hydrate forms with arsenious acid a compound, $FeAsO_3$, which is much less soluble in the gastric secretions than the acid alone:

$$Fe_2(OH)_6 + As_2O_3 = 3H_2O + 2FeAsO_3.$$

MAGNESIA only slightly calcined, forms with arsenic a compound which is not readily soluble in the intestinal canal. It has for this reason been recommended and used as an antidote.[2] Ordinary calcined magnesia has, however, little effect in this way unless quite recently prepared, for when kept, it absorbs carbonic acid from the air. It may, nevertheless, be used, in an emergency, a large teaspoonful being given in two or three ounces of water every ten minutes. When the contents of the stomach are alkaline, the arsenic circulating in the blood acts less rapidly and energetically on the mucous membrane of the stomach, than under other conditions.

It is quite possible that, in the treatment of arsenical poisoning, too little is done to lessen THE PAIN in the stomach, which is very severe and exhausting. As the records show, physicians, under the excitement and novelty

[1] Bunsen und Berthold, 'Das Eisenoxydhydrat, ein Gegengift der arsenigen Säure,' Göttingen, 1834.

[2] Bussy, 'Compt. rend. de l'Acad. des Sc.,' 1846, Bd. xxii, S. 845; B. Schuchardt, 'Untersuchungen über die Anwendung des Magnesiahydrats gegen Arsenik und Quecksilberchlorid,' Göttingen, 1852.

of the position, give Bunsen's antidote after the prescribed fashion, in cupfuls, long after the poison has passed out of the stomach, and at the post-mortem examination large masses of the remedy are found there, which, merely as foreign bodies, must have had an injurious effect on the eroded mucous membrane. In my opinion, the proper mode of treating these cases, when gastric inflammation exists, is to encourage vomiting by giving lukewarm water with a little magnesia suspended in it, and in this way to wash out the stomach; to let the patient afterwards have small pieces of ice to swallow, and to administer hypodermically small doses—0·005 gramme ($\frac{1}{15}$ of a grain)—of morphia. When gastritis exists it is not advisable to wash out the stomach with an œsophageal tube, highly serviceable though this may be in other forms of poisoning.

Arseniettted hydrogen, AsH_3, is sometimes productive of poisonous effects in laboratories or workshops. This may happen especially in the preparation of hydrogen if either the zinc or acid employed, or both, contain any large amount of arsenic,—and this is almost invariably the case with the cheap commercial sulphuric acid. Arseniotted hydrogen is extremely poisonous. In 1815 the chemist A. F. Gehlen, of Munich, died from its effects. When preparing the gas and smelling its odour he carelessly inhaled too large a quantity. He was immediately seized with nausea, vomiting, and great exhaustion, and died at the end of nine days.[1] The chemist Brittan, of Dublin, was poisoned in the same way, as well as Hans Schulze, professor at Santiago, in Chili, as recently as November, 1892. In addition to these instances a large number of other cases of poisoning by the gas have been recorded.[2] The symptoms generally produced are vomiting, pain in the

[1] Buchner, 'Toxikologie,' 1827, S. 476.

[2] Unter andern: Schindler, ref. 'Jahrb. der ges. Med.,' Bd. xxiv, S. 165; J. Vogel, 'Arch. f. wissensch. Heilk.,' 1854, Bd. i, S. 209; Ollivier, 'Gaz. des hôp.,' 1863, S. 509; Trost, 'Vierteljahrschr. f. gerichtl. Med.,' 1873, Bd. xviii, S. 269; Wächter, ibid., 1878, Bd. xxviii, S. 251; Eitner, 'Berliner klin. Wochenschr.,' 1880, S. 256; Coester, 'Berl. klin. Wochenschr.,' 1886, S. 209; Schickhardt, 'Münch. med. Wochenschr.,' 1891, S. 26.

region of the stomach, prostration with headache, jaundice and hæmaturia—the urine sometimes being "as black as ink." The case runs on slowly, and generally terminates fatally. The jaundice originates in the liver, and is due to disintegration of the blood, the bile produced from which is more readily absorbed[1] than under normal conditions. The arseniettted hydrogen destroys the red blood-corpuscles and decomposes the oxyhæmoglobin.[2] The effect on the latter, as shown by spectrum analysis, is the same as is observed after the action of ozone, and of sulphuretted hydrogen, and also in putrid blood, a dark band appearing in the red in the place of that of methæmoglobin.

The rapidity and intensity of the poisonous effects produced by arsenietted hydrogen are due in the first place to the fact that it is in a gaseous form, and is consequently readily absorbed when inspired, and, passing directly into the blood, its action is spread over a large area; secondly, to the large percentage—not less than 96·15—of arsenic which it contains; one cubic centimetre ($\frac{1}{16}$ of a cubic inch), at a pressure of 760 mm. and 0° C., containing as much metallic arsenic as corresponds with 0·0044 gramme ($\frac{1}{15}$ of a grain) of arsenious acid; and thirdly, to the extreme readiness with which it is decomposed.

We may readily assume, therefore, that in the organism the hydrogen immediately assumes the nascent state, and together with the arsenic is oxidised at the expense of the oxyhæmoglobin and the living cellular protoplasm, and that the rapidity with which this reduction takes place (nascent oxygen[3] being at the same time liberated) causes the destruction of the tissue. As is well known, pyrogallic acid, which is a powerful reducing agent, acts in a precisely similar manner, destroying the red blood-corpuscles and paralysing the nervous centres. The effect only differs quantitatively, for the pyrogallic acid does not abstract the oxygen so energetically as the arsenietted hydrogen, nor

[1] Stadelmann, 'Arch. f. exper. Path. u. Pharmak.,' 1882, Bd. xvi, S. 221.

[2] Koschlakoff und Bogomoloff, 'Centralbl. f. med. Wiss.,' 1868, S. 627; Hoppe-Seyler, 'Zeitschr. f. physiol. Chemie,' 1877, Bd. i, S. 134.

[3] Hoppe-Seyler, loc. cit., Bd. ii, S. 22.

does it, to any appreciable extent, develop any new poison in the system, as does arsenious acid. In every other respect, however, we get a clearer idea of the action of arseniettted hydrogen by comparing its chemical properties and poisonous effects with those of pyrogallic acid.

The formation of gaseous arsenietted hydrogen by a different method from the one previously described, possesses considerable interest for the physician. We are familiar with the chronic forms of poisoning which result from the use in rooms of green pigments containing arsenic; the poisoning may result from these colours passing off as dust and lodging for a longer or shorter period in the nose and mouth. But it may also be developed by the decomposition of the arsenical oxide by means of hyphomycetes or mould fungi, which grow on damp walls and, reducing the oxide, develop arsenietted hydrogen.

The bright green colour most usually employed is Schweinfurt or imperial green, a compound of arsenite and acetate of copper with a variable amount of free arsenious acid. H. Fleck has demonstrated, what had been previously assumed from the alliacous odour of these apartments, that the arsenious acid is reduced by the mould fungus, and that as a result the gas now under consideration is produced.[1] If even small quantities of this are inhaled for some time, especially in sleeping rooms, we can easily understand the development of the very various forms of discomfort, of which numerous descriptions have been published. I will here only refer to the observations published by G. Kirchgässer,[2] of Coblentz, who within four years treated 21 cases of this kind. In eight of these the urine was tested chemically for arsenic, and its actual presence determined in six instances; in the remaining cases the cause was ascertained by removing the sufferer from the suspected locality. Kirchgässer, as well as other authors, also discovered that the paint or wallpaper was still actively poisonous even when covered with another coat of paint or another paper.

[1] H. Fleck, "Der Arsengehalt der Zimmerluft," 'Zeitschr. f. Biol,' 1872, Bd. viii, S. 444.

[2] G. Kirchgässer, 'Vierteljahrschr. f. gerichtl. Med.,' 1868, Bd. ix, S. 96.

The following case[1] is instructive, and many similar ones have been observed. A teacher had suffered for several years from migraine, which was generally felt on awaking in the morning. After a time he was also troubled late in the evening with headache disturbing his sleep and developing in the morning into migraine. At first the discomfort passed off in the course of the forenoon, but after a time it became continuous, and was accompanied with nausea and loss of appetite. Symptoms of the same kind but in a lesser degree appeared in two of the students, who in the evening worked at the same table with their teacher. The consequent suspicion that there was a common cause for these symptoms led to an examination of the green shade of the petroleum lamp, which was found to contain a large amount of arsenic; it was removed, and in a few days the typical symptoms and gastric troubles of the three individuals ceased. The reason why the symptoms were most marked in the teacher was that he was short-sighted, and in order to see more distinctly was accustomed to sit much nearer to the lamp than either of the others.

It is easy for a physician in cases where some chronic disorder is supposed to be due to a wall paint, paper, garment,[2] or lamp-shade, to determine whether arsenic is present or not without any special chemical apparatus. A. Bettendorf [3] has described a simple and effective method of doing this.

I put into this dry test-tube a few cubic centimetres of fuming hydrochloric acid, add a few crystals of stannous chloride, and heat the mixture; I wait till the contents of the tube are cold, and if the solution remains colourless I know that my reagents are pure and free from arsenic. I now drop into the solution a small piece of paper the size of a sixpence, coloured with Schweinfurt green, and again heat it. During the process the pellucid liquid becomes yellow and cloudy, and on cooling is brown and opaque. On

[1] N. Zuntz, 'Sitzungsber. d. Niederrhein. Ges. in Bonn,' 1875, S. 127.

[2] Riedel, "Arsenvergiftung durch Tarlatankleiderstoff," 'Berl. klin. Wochenschr.,' 1870, S. 471.

[3] A. Bettendorff, 'Zeitschr. f. Chemie,' 1869, Jahrg. 12, S. 492; 'Sitzungsberichte d. Niederrhein. Ges. Bonn,' 1869, S. 128.

allowing it to stand an arsenical mirror is deposited on the side of the tube. These changes may be expressed by the two following formulæ:

$$As_2O_3 + 6HCl = 3H_2O + 2AsCl_3.$$
$$2AsCl_3 + 3SnCl_2 = 3SnCl_4 + 2As.$$

That is to say, the arsenious acid is, by means of the hydrochloric acid, converted into trichloride of arsenic, which, on the addition of the stannous chloride (the latter being converted into stannic chloride), is reduced to metallic arsenic. This is absolutely insoluble in the hydrochloric acid, and renders it brown and opaque. The hydrochloric acid must be of such strength as to give off fumes on opening the bottle; the officinal acid will not produce the reaction. The stannous chloride must have been kept in a well-stoppered bottle, as on exposure to the air it is gradually oxidised into stannic chlorate and stannic acid. Moreover it is only the two oxides of arsenic which give this reaction; its other compounds must, therefore, be first converted into the oxides by ignition with potassium chlorate and soda. Lastly, a brown discoloration may also be developed if the specimen which we are testing for arsenic contains either gelatine or albumen; this discoloration, however, differs from that produced by arsenic in being extremely slight, and in such a case it is well, for the sake of comparison, to make another experiment with a few particles of arsenic. The presence of any ordinary metallic substances with the arsenic produces little or no difference in the reaction, as they are dissolved in the liquid. Quicksilver, gold, and platinum yield dark precipitates; but irrespective of the fact that platinum alone gives the black-brown precipitate similar to that of arsenic, these metals are not likely to be present under the conditions which we are discussing. One other exception will be referred to in dealing with subnitrate of bismuth.

The investigation may also be made by dissolving a small piece of pure tin in hydrochloric acid, thereby forming stannous chloride, in the event of a pure specimen of the latter not being procurable.[1]

[1] H. Heubach, 'Berliner klin. Wochenschr.,' 1876, S. 353.

XX.

Subnitrate of bismuth—Its use in gastralgia and intestinal catarrh—Its toxicology—Preparations of lead—Their therapeutic use—Symptoms of lead poisoning—Analysis of the more important—Treatment of lead poisoning—Nitrate of silver—Historical details—Its use externally and internally—Discoloration of the skin resulting from its internal administration—Acute and chronic poisoning—Chloride of gold.

BISMUTH belongs to the same chemical group as phosphorus and arsenic, and has a certain similarity in its therapeutic effects to those of the officinal oxide of the latter.

The SUBNITRATE OF BISMUTH is a heavy white powder in minute crystalline scales, having an acid reaction. When ignited it gives off orange-coloured fumes of nitric oxide, leaving a residue of about 80 per cent. which consists of oxide of bismuth. The subnitrate is insoluble in water, but forms a clear and colourless solution with sulphuric acid. It consists of a mixture of two basic nitrates:

$$(Bi[HO]_2.NO_3) + (BiO.NO_3 + BiO.OH).$$

It was first prepared about the end of the seventeenth century by N. Lemery, a chemist, who sold it as a secret remedy for spasms of the stomach, and for migraine. It only came into general use by physicians after the publication of a treatise by L. Odier,[1] in Geneva, in 1786, 'Observations sur les effets du magistère de bismuth donné intérieurement comme antispasmodique.' Since that time it has been continuously used as a remedy, more particularly in cases of gastralgia and intractable diarrhœa.

As regards the first class of disorders, the use of sub-

[1] L. Odier, 'Journal de méd. chir. pharm., &c.,' Paris, vol. lxviii, p. 49.

nitrate of bismuth is particularly indicated in those forms of gastric uneasiness of a purely nervous origin which occur in hysterical and badly nourished individuals, in whom the use of condiments causes pain and vomiting; it is also employed in the vomiting of pregnancy and in the gastralgia which accompanies ulcerative changes in the stomach. With regard to the second class of disorders, it has been stated that this remedy acts better than any other,[1]—in fact, almost as a specific in those cases of diarrhœa which are dependent upon follicular and dysenteric ulceration; in simple catarrhal and in tuberculous disorder it is of no service.

Experiments on animals have shed some light upon the poisonous effects of bismuth, but they have failed to afford any explanation of its therapeutic properties; possibly the clue to the explanation of the latter is to be sought for in an entirely different direction.

For a considerable period the subnitrate of bismuth suspended in water has been employed by some physicians, in infectious catarrh of the urethra, and as an application to offensive ulcers. The results of its employment in this way may account for the fact that the surgeons of the present day have used it as an antiseptic. Some of them have reported very favorably of its effects.[2]

The subnitrate acts as a good antiseptic,—not, however, for fluids, but only when applied directly to the tissues. The simple explanation of this is its insolubility in water; it settles at once to the bottom, and therefore can exert no effect on the supernatant liquid. Any albumen which may be precipitated with it remains undecomposed, for the two are in continuous contact. This is also the case when it is applied to the mucous membrane of the urethra, where it comes in contact with and paralyses the gonococci. Also when sprinkled on recent wounds it prevents the development of any putrefactive change.

This antiseptic action may arise from two causes, the first of which is the separation of nitric acid. If I shake up

[1] Nothnagel und Rossbach, 'Handbuch der Arzneimittellehre,' 1884, S. 254.

[2] Riedel, 'Centralbl. f. Chirurgie,' 1883, Beilage zu No. 23, S. 3; O. Petersen, 'St. Petersburger med. Wochenschr.,' 1884, No. 21.

in a test-glass a few grammes of subnitrate of bismuth with a little water, the latter immediately acquires an acid reaction; and if I pour off the supernatant water, add fresh, and again agitate the mixture, the same result takes place, even though the process is repeated several times. Free acid is therefore, for a certain period, continuously liberated from the salt. The same result must take place, although in a lesser degree, when this substance is brought in contact with the serum exuding from that portion of the body to which it is applied. Nitric acid, however, is an energetic germicide, and this may explain many clinical results,—with the proviso, of course, that the bismuth compound is present to such an extent as to overcome the alkalinity of the serum.[1]

In the second place, results may be induced by bismuth similar to those which arise from arsenic, to which it is so closely allied. The oxides of bismuth may induce a transference of nascent oxygen. The suboxide of bismuth, Bi_2O_2, rapidly absorbs oxygen from damp air, and is converted into the teroxide, Bi_2O_3. A further stage is the pentoxide, or bismuthic anhydride, Bi_2O_5; this when heated is decomposed into Bi_2O_3+O+O. To this labile condition of its oxygen the antiseptic action of bismuth may possibly be due. This, however, must be determined by experimental investigation.

It can be readily imagined that this antiseptic action may be usefully employed in certain conditions of the stomach and intestines. All antiseptic substances when employed at the proper time, and in suitable form, can act as sedatives to inflamed tissue; and where ulcerative inflammatory conditions of the internal coat of the intestinal canal depend upon the presence of putrid matter, or are complicated and intensified thereby, it is quite possible that an antiseptic, by covering over the intestinal wall, produces effects equally beneficial to those which result from its application to the mucous membrane of the urethra when inflamed by the action of micro-organisms.

I must also refer to another explanation[2] which has been

[1] Gosselin and Héret, 'Centralbl. f. d. med. Wiss.,' 1886, S. 374.

[2] Bókai (Klausenburg), "Ueber die Wirkung der Darmgase auf die Darmbewegungen," 'Centralbl. f. klin. Med.,' 1885, S. 134.

offered with regard to the action of bismuth on intestinal catarrh. It was suggested by the results of certain experiments made on rabbits. Sulphuretted hydrogen is one of the gases by which violent peristaltic movements of the intestine can be induced; if an increased amount of this gas is developed in any intestinal disorder, as the result of putrefactive or fermentative changes, it is absorbed by the bismuth, and converts the latter into sulphide, and in this way the increased peristalsis is reduced.

Riedel has made the following statements regarding the effect of the subnitrate of bismuth in the treatment of wounds. Notwithstanding its insolubility it has a corrosive action. It causes adhesive inflammation of the pleura and peritoneum, and may even cause perforation of the intestine if this is thickly coated with it, and must therefore be used here with great caution. On wounds in general it has no corrosive action, but when they are extensive, greatly promotes their healing by the first intention. After irrigation of wounds with a 2 to 10 per cent. mixture of bismuth, some portion is evidently absorbed in a soluble form by the wound, for acute stomatitis, enteritis and nephritis have been known to occur after its application. These were accompanied by distinct bluish-black or brownish discoloration of the tissues,[1] dependent possibly on similar discoloration of the binoxide and teroxide.

These results agree on the whole with those obtained from experiments on animals.[2] As small a quantity as 8 milligrammes of the ammonio-citrate of bismuth produced in a rabbit poisonous symptoms similar to those resulting from arsenic. It must not, however, be overlooked that this only occurred when it was employed subcutaneously.

This reminds me that it has frequently been stated that the salts of bismuth alone are not poisonous, and that in cases where poisoning has occurred it has resulted from the bismuth being contaminated with arsenic. The experiments above referred to nevertheless prove, so far at least as the

[1] F. Petersen, 'Deutsch. med. Wochenschr.,' 1883, S. 365.

[2] Feder-Meyer, 'Rossbach's Pharmakol. Untersuch.,' 1882, Bd. iii, S. 235; Luchsinger, 'Berner Mitteil.,' 1883, No. 1060, S. 26; H. Meyer and Steinfeld, 'Arch. f. exper. Path. u. Pharm.,' 1885, Bd. xx, S. 40.

external application of the remedy is concerned, that this view is incorrect, for in these experiments chemically pure preparations only were employed. Poisoning nevertheless has occurred from such contamination, but that was before official directions had been given that the preparations of bismuth should be absolutely free from any trace of arsenic. In the native minerals containing bismuth, arsenic is usually present, and is only separated from the bismuth with considerable difficulty, and moreover, unless the bismuth from which its different compounds are prepared is free from arsenic, they will be found to contain this impurity. Taylor tested samples of the subnitrate obtained from three leading druggists, and found that arsenic was present in comparatively large quantities; out of five specimens only two were free from it. To this impurity are due the somewhat numerous cases of fatal poisoning which have followed the administration of ordinary doses of the subnitrate.

Bettendorf's test for arsenic, which I have already demonstrated to you (see p. 97), is that by which the presence of this substance may be most readily detected in any of the preparations of bismuth. It has happened, however, that on testing a specimen of subnitrate of bismuth in the above manner, a black precipitate was formed, although no arsenic was present. This was due to the presence of a small amount of tellurium, in the form either of tellurious or telluric acid. Both these acids are decomposed by Bettendorff's test, the tellurium being thrown down as a black precipitate; this reaction takes place very distinctly even if only slight traces of the metal are present.[1]

The salts of bismuth are also sometimes contaminated with lead. This has caused symptoms of lead poisoning in persons who for some time have used basic carbonate or chloride of bismuth as a cosmetic, and have allowed some of the powder to pass accidentally into the mouth.

Thirty-six hours after administering a gramme of subnitrate of bismuth to a goat, the metal appeared in the animal's milk,[2] but after seventy-two hours no trace could be detected. The total amount recovered was exceedingly small.

[1] H. Klinger, 'Verhandl. d. Niederrhein. Ges. zu Bonn,' 2 Juli, 1894.
[2] G. Lewald, 'Uebergang von Arzneimitteln in die Milch,' 1857, S. 5.

The fact that the remedy only possesses a local action is probably the reason why the dose is comparatively large—the amount that should be given in the twenty-four hours being, as the result of clinical experience, from 1 to 5 grammes (15 to 75 grains).

The fæces may become, from the resulting sulphide of bismuth—Bi_2S_3,—of a grey or black colour. Sometimes after the administration of the subnitrate of bismuth, the breath has an offensive and garlic-like odour. This is due to the salt being contaminated with traces of tellurium or its oxide.[1] Tellurium is converted in the organism into the volatile methyl telluride, which has this characteristic odour.[2]

With regard to the external employment of subnitrate of bismuth, we must not omit to mention that it is a useful application to extensive burns.[3] It is mixed with sterilised (boiled) water so as to form a thick paste, with which the burns are painted by means of a soft brush. This forms a covering impervious to air, any cracks or fissures afterwards formed being remedied by a further application of the paste. Traces of the bismuth may be absorbed by the wounds, and appear in the urine together with traces of albumen, but the application is said to have a most beneficial effect in promoting the healing of the burns, which takes place within ten to fourteen days. None of the characteristic poisonous effects of bismuth are developed even when the remedy is applied over a considerable surface.

Bismuthi Subsalicylas, subsalicylate of bismuth—$Bi(C_7H_5O_3)_3.Bi_2O_3$,—is now frequently employed instead of the subnitrate, and is said to produce better results. It is a white, odourless, and tasteless amorphous powder, and is insoluble both in water and in rectified spirit.

It is employed in chronic disorders of the stomach and intestines, as well as in typhoid fever. The dose is from 0·3 to 1·0 gramme (4½ to 15 grains) three or four times a day or oftener. It is readily tolerated; as much as

[1] W. Reisert, 'Arch. der Pharmacie,' 1884, S. 511.

[2] F. Hofmeister, 'Arch. f. exper. Path. u. Pharmak.,' 1894, Bd. xxxii, S. 202.

[3] Bardeleben, 'Deutsch. med. Wochensch.,' 1890, S. 437; C. Orthoff, ibid., 1893, S. 931.

10 grammes (150 grains) have been taken in the twenty-four hours without inconvenience. As it is now frequently prescribed it has recently been included in the German pharmacopœia.

For several centuries, preparations of LEAD have been employed therapeutically, both externally and internally; apparently physicians came to employ it as an internal remedy from observing some of its poisonous effects, namely, that it rendered the pulse hard and tense and caused obstinate constipation of the bowels.

The former of these results was supposed to depend on spasm of the arterial wall. For this reason it was expected that great benefit would be derived from the administration of lead in hæmorrhages from internal organs, especially from the lungs and kidneys, with which the metal, in a state of solution, would be brought in contact through the medium of the circulation. For nearly fifty years lead was almost invariably given in hæmorrhage of the lungs due to consumptive mischief. At the present day this is scarcely ever done. There was no proof that the improvement in such cases was not independent of the action of the lead, and this doubtful benefit was more than counterbalanced by the injurious effects which the remedy almost invariably produced on the system in general. On the other hand, in hæmorrhages from the stomach and intestines there can be no room to doubt its beneficial results.

It is still used as an astringent agent, more particularly in obstinate forms of diarrhœa depending upon ulceration of the intestinal mucous membrane. In such conditions acetate of lead and opium are the remedies generally employed.

With this general reference to the therapeutic use of lead internally, we will now proceed to discuss in detail its toxicological effects.

As lead is used so largely both for domestic purposes

and in the arts, and more especially in the manufacture of various colouring materials, such as red lead, litharge, and white lead, there is abundant opportunity for studying its poisonous action. The dust of its various preparations fills the workrooms and gets on to the hands and into the mouths of the workmen; and though each day this may take place only to a slight extent, after a short period the total amount absorbed is quite sufficient to develop the poisonous effects of the mineral on the system.

The first and most characteristic symptoms are as follows: the patient has a general cachectic appearance, and complains of a metallic taste in his mouth; the gums present a dirty grey discoloration, and there is severe colic. In eighty-six cases examined by Riegel,[1] eighty-two complained of colic.

That lead should produce its effects upon the nutrition in general, upon the blood, and upon the tissues, is easily intelligible from the fact that it is readily absorbed from the alimentary canal, and passing, probably in the form of an albuminate, into the circulation, is deposited in the tissues themselves. Even when the lead produces fatal results no lead is found in the blood serum, and very little even in the blood-corpuscles. In the nerve centres, however, according to E. Heubel,[2] a large amount is deposited, more than in any other parts of the body, with the exception of the two excretory organs, the liver and kidneys,[3] and the bones.

It is antecedently impossible that this foreign metallic body could, with its astringent and corrosive properties, be in contact with these nervous centres without producing very distinct effects. In one case which ran a very chronic course, degeneration of small portions of the nervous structure was discovered microscopically.[4] Hyper-

[1] A. Frank, 'Arch. f. klin. Med.,' 1875, Bd. xvi, S. 423.

[2] Heubel, 'Pathogenese u. Symptome d. chron. Bleivergiftung,' 1871.

[3] Prevost and Binet, 'Revue méd. de la Suisse rom.,' 1889, Nos. 10 and 11.

[4] Kussmaul and Maier, "Pathologische Anatomie des chronischen Saturnismus," 'Arch. f. klin. Med.,' 1872, Bd. ix, s. 283; R. Meier, 'Arch. f. pathol. Anat.,' 1882, Bd. xc, s. 455; Robinson, ref. 'Cbl. f. klin. Med.,' 1895, S. 328.

trophy and sclerosis of the connective tissue were observed in several of the sympathetic ganglia, more especially in the cœliac and upper cervical ganglia, together with induration, diminished vascularity, and a decrease in the cellular nerve elements of these organs. Chronic degeneration of the gland cells and of the vessels was found in the stomach and intestines of animals which had suffered from chronic lead poisoning. We may assume that changes in the cellular protoplasm, similar to those above described, always take place when the nerve centres in general are acted upon by lead. STIMULATION, MORBID GROWTH, and PARALYSIS of the cells are induced either successively or concurrently, thus explaining the distinctly localised but variable effects which result from the disturbances of the nervous system.

Pains differing widely in character, and affecting the most diverse parts of the body, tremulousness first affecting the limbs and then gradually extending to the whole body, paralysis followed by atrophy of single groups of muscles, anæsthesia, amaurosis or amblyopia, asthma, delirum, mental derangement either of a melancholic or maniacal character, attacks of unconsciousness together with epileptic convulsions, all these effects are more or less rapidly produced by the poisonous action of lead upon the nervous protoplasm. The nutritive process and the intestinal organs are generally the earliest affected; the cerebral cortex is the last to suffer.

These results have been confirmed by numerous experiments on animals.[1] The effects of lead on the various animal species differ considerably, and there is a marked difference between its effects on animals in general and on man. It has been observed that lead also acts upon striated muscular tissue, causing the muscles to be more easily exhausted, and to become finally insensible to stimulation. The muscle is quickly fatigued, a few contractions, or even a single one, being enough to render it incapable of further action for a considerable time. The induced current then produces no effect. The muscles are pale and atrophied. A microscopical examination reveals proliferation of the

[1] E. Harnack, 'Arch. f. exper. Path. u. Pharm.,' 1879, Bd. ix, S. 152.

nuclei and wasting of the muscular fibres, as well as degeneration of the nerve fibres.[1]

Lead colic is said to be caused by violent contraction of the bowel, the peritoneal covering being sympathetically affected. The irritation of the intestinal ganglia produces constipation in the human subject, whereas generally in animals it increases considerably the peristaltic action of the bowels, causing diarrhœa. The retraction and hardness of the abdominal parietes are produced by reflex spasms of the abdominal muscles.

Clinical observations[2] on the human subject have shown that if a patient suffering from lead colic inhales nitrite of amyl, the abnormal tension of the pulse decreases very rapidly and is replaced by a relaxed state of the arteries. With this the pain immediately subsides, but only to recur with the return of the increased vascular tension, as the effect of the nitrite upon the vessels passes off. Dilatation of the vessels by means of pilocarpin[3] produces the same result. The pain is therefore due to morbid stimulation of the vaso-motor nerves and of the vascular walls.

Albuminuria occurs both in acute and chronic lead poisoning, but not so constantly as the other symptoms. It was present in a case of acute poisoning from red lead which came under my own observation. The patient, who was an attendant at the Institute, had been blowing down gaspipes coated with red lead, and for several days had taken his meals when his fingers were smeared with it. He was seized with violent and painful diarrhœa, passed blood in his motions, was affected with fœtid stomatitis and albuminuria, and had the usual blue line on the gums. The symptoms continued only four or five days, the stomatitis being of longest duration. The presence of lead was clearly recognisable in the urine, after incinerating the residue left by evaporation. The disease may even give rise to contracted kidney.[4]

Under normal conditions very little of the absorbed lead

[1] C. Friedländer, 'Arch. f. path. Anat.,' 1879, vol. lxxv, p. 24.
[2] Riegel, 'Arch. f. klin. Med.,' 1878, vol. xxi, p. 201.
[3] E. Bardenhewer, 'Berl. klin. Wochenschr.,' 1877, S. 125.
[4] W. Lublinski, 'Deutsche med. Wochenschr.,' 1885, S. 337.

is eliminated in the urine, even in cases of chronic poisoning. On the other hand, if albuminuria is already present, the elimination of lead by the kidneys appears to be increased, while at the same time the albuminuria is modified by the lead. This point has been investigated by Lewald.[1] He gave a young man suffering from chronic Bright's disease on the first day 0·1 gramme (1½ grains), on the second 0·3 gramme (4½ grains), and on the third 0·42 gramme (6·3 grains) of acetate of lead. The quantity of urine secreted on these three days and on the one immediately following was INCREASED 45 per cent., as compared with that of the three previous days, while on the other hand the entire amount of albumen excreted DECREASED 12·9 per cent. In a second series of experiments on the same patient with acetate of lead in smaller doses, the increase in quantity was again very marked. In each case the urine contained lead, and a larger amount of fibrinous casts corresponding with the copious diuresis. Lewald attributes this to an astringent effect exercised by the lead upon the relaxed and obstructed vessels and tubules of the kidneys. The lead was found in the albumen, precipitated from the urine, and not in the filtrate.

The greatest amount of lead is eliminated by the intestinal canal, the bile containing a large portion of it. By the action of hydrogen sulphide the albuminous compounds are there converted into the albuminate of lead sulphide, and appear in this form in the fæces. According to Lewald, lead is also eliminated in the milk. After giving 1·2 and 0·6 gramme (18 and 9 grains), he could detect its presence in the milk for six days. Here we have an example of the retention of lead in the system such as is sometimes observed in patients who suffer from the effects of lead poisoning some considerable time after they have been exposed to its action.

PLUMBUM ACETICUM, Plumbi cetas, Acetate of lead, the only preparation used internally, consists of colourless transparent crystals or crystalline masses, which have a faint odour of acetic acid and are soluble in 2·3 parts of water,

[1] G. Lewald, "Ueber die Ausscheidung von Arzneimitteln, u. s. w.," 'Jahresber. d. Schles. Ges. Naturw.-Med. Abt.,' Breslau, 1861, p. 236.

and in 29 parts of spirits of wine. The watery solution has a sweetish, astringent taste, and gives a black precipitate on the addition of hydrogen sulphide, a white precipitate with sulphuric acid, and a yellow precipitate with potassium iodide. Its formula is $Pb\,(C_2H_3O_2) + 3H_2O$, the maximum single dose is 0·1 gramme (1½ grains), the maximum amount to be given in the day is 0·5 gramme (7½ grains). The reason for limiting the doses to these quantities is that some persons are extremely sensitive to the action of lead, and its administration to them may very readily cause stomatitis, gastritis, and either painful diarrhœa or constipation, &c.[1]

Three parts of acetate of lead triturated with one of litharge (PbO), and 10 parts of water, and boiled, form

Liquor Plumbi Subacetici, solution of subacetate of lead. This is a clear, colourless liquid with a sweet, astringent taste and alkaline reaction. Its specific gravity is from 1·235 to 1·240. If exposed to the air it becomes turbid, owing to the absorption of carbonic acid, and the formation of insoluble carbonate of lead. The composition of this preparation is substantially $Pb_2.(C_2H_3O_2)_4 + Pb(OH)_2$.

Solution of subacetate of lead immediately precipitates albumen, and consequently in an undiluted form acts as a caustic. When diluted it dries the tissues, checks the secretions, and paralyses micro-organisms, and owing to these qualities it is useful in various ways as an external application. It is most commonly employed in the form of

Aqua Plumbi, lead lotion. This is prepared by mixing together 1 part of the solution of subacetate of lead with 49 of water. It is slightly turbid, owing to the presence of a little carbonate of lead, which is formed by the absorption of carbonic acid from the air. Its action is essentially the same as that of solution of the subacetate of lead, only much milder, the natural result of its dilution.

Alkalies, the alkaline carbonates, hydrochloric and sulphuric acids, the chlorides and sulphates, as well as mucilaginous and albuminous substances, are incompatible with the

[1] R. Pick, 'Deutsche med. Wochenschr.,' 1878, S. 452. An account of poisonous effects being produced twice after doses of 0·09 and 0·06 gramme (1⅓ and $\frac{9}{10}$ of a grain). Unfortunately it is not proved that no mistake was made by the chemist as to the weight.

two preceding solutions, owing to the formation in the mixture of insoluble precipitates.

AQUA GOULARDI, Goulard's lotion, was the name given to a former officinal preparation, which consisted of lead lotion to which some rectified spirit had been added. About the year 1760 Goulard made an "Extrait de Saturne" by boiling oxide of lead in vinegar. Putting a teaspoonful of this solution, with twice the amount of brandy, into a bottle of water, he prepared what he called "Aqua vegeto-mineralis." Under certain conditions the addition of rectified spirit may prove beneficial.

The following preparations of lead are also used externally:

UNGUENTUM PLUMBI, lead ointment, which is made of two parts of Liquor Plumbi Acetici and nineteen parts of vaseline.

UNGUENTUM PLUMBI TANNICI, ointment of tannate of lead. Tannic acid is added to solution of subacetate of lead; the whole is then mixed with lard to form an ointment. It is yellowish in colour. A paste of tannate of lead with water was recommended by Autenneth of Tübingen in 1816 as a preventive against bedsores, but has now been superseded by better modes of treatment.

UNGUENTUM CERUSÆ, ointment of white-lead, consists of a mixture of three parts of finely pulverised white-lead with seven parts of vaseline. Cerusa is the ancient Latin name for what we now call white-lead; it was prepared by the ancients, and used, among other purposes, as a cosmetic, the ψιμύδιον of the Greeks. Its chemical composition is $2PbCO_3+Pb(OH)_2$, the basis being lead carbonate. It appears either as a white, heavy, easily discoloured powder, or in pieces which are readily pulverised. It is insoluble in water or alcohol, but soluble with effervescence in diluted nitric and acetic acids. It is used as an absorbent in the form of fine powder, and as an ointment to ulcerated surfaces. Triturated with 5 per cent. of camphor it forms the officinal UNGUENTUM CERUSÆ CAMPHORATUM, an ointment very well adapted for the prevention of bedsores.

There are also the following preparations:—EMPLASTRUM CERUSÆ, white-lead plaster. This is lead plaster boiled with

white-lead and olive oil, and is white in colour. EMPLASTRUM FUSCUM CAMPHORATUM, finely powdered red-lead, is boiled in olive oil, and then wax and camphor are added. It has a dark brown colour, and smells of camphor.

EMPLASTRUM LITHARGYRI, Empl. Plumbi Diachylon s. simplex, lead or diachylon plaster. Equal parts of olive oil, lard, and oxide of lead are boiled together in water until the product acquires a proper consistence for a plaster. It is white and tough, not greasy, and consists essentially of lead oleate and palmitinate. It forms the ordinary basis of most plasters. EMPLASTRUM LITHARGYRI COMPOSITUM, adhesive plaster, is the same as the preceding, with the addition of ammoniacum, galbanum,[1] turpentine, and yellow wax. It is at first yellowish in colour, and afterwards becomes darker. UNGUENTUM DIACHYLON, diachylon ointment, is simply lead-plaster melted down in olive oil. It is almost white.

LITHARGYRUM, litharge, is simply oxide of lead, PbO, a heavy yellowish or reddish-yellow powder, insoluble in water, but forming, when dissolved in dilute nitric acid, a colourless solution. MINIUM, red-lead, is composed of oxide and peroxide of lead, $2PbO+PbO_2=Pb_3O_4$. It is a bright red powder, insoluble in water. It readily parts with the one atom of oxygen in the peroxide of lead, PbO_2, to various oxidisable substances. Red-lead turns tincture of guaiacum blue, and decomposes a neutral solution of potassium iodide in a few minutes, instantaneously if the solution of iodide of potassium has been acidulated, and contains hydriodic acid. Following the precedent set by Schönbein, it was formerly the custom to call chemical compounds which operated in

[1] Galbanum, a gum-resin from Persian plants belonging to the genus *Ferula*, Nat. Ord. Umbelliferæ. The gum-resin exudes from the stems and is then refined. It consists of greenish or brownish-yellow masses containing an ethereal oil, the chief ingredient of which is isomeric with camphor.

Ammoniacum, another gum-resin, obtained from *Dorema ammoniacum*, a Persian umbellifer. It occurs as yellowish-brown tears or masses, which become soft when heated, and which consist of gum-resin and volatile oil, neither of which contains any trace of sulphur. On heating ammoniacum and galbanum with caustic potash we obtain resorcin, $C_6H_4(OH)_2$.

this fashion ozone carriers. It is now known that they carry no actual ozone, but, as is the case with ozone, a single and easily liberated atom of oxygen with two unsaturated affinities. Such oxygen is called atomistic, active, or nascent.

Metallic lead is oxidised when exposed to damp air. Exposed in a minutely divided form it is quickly converted into the suboxide of lead, Pb_2O. This, acted upon by oxidising acids, is converted into the oxide, PbO, and metallic lead. Oxide of lead readily gives off a portion of its oxygen to oxidisable substances. If we treat the next higher oxide, the sesquioxide, Pb_2O_3, with acids, we obtain the oxide and peroxide, $Pb_2O_3 = PbO + PbO_2$, with the properties of which, as existing in minium, we are already familiar. It is probable that the affinity of lead for oxygen is of importance, not only from a technical point of view (as an illustration of which I would refer to the rapid hardening and drying of oil-colours by the addition of preparations of lead), but also in pharmacology.[1]

In the treatment of acute poisoning from lead, where it is probable that the poison is still in the stomach, the first thing to be done is to give some substance which will convert it into an insoluble compound. If to a clear solution of acetate of lead I add some diluted sulphuric acid, or a solution of sulphate of soda or magnesia—that is to say, of Glauber's or Epsom salts—a precipitate of sulphate of lead is immediately formed, which at all events is less easily absorbed than the acetate of lead from the stomach and intestines. White of egg or milk may also be given, but of course not at the same time as the sulphuric acid or the sulphates. The diarrhœa, stomatitis, albuminuria, &c., must be treated on general principles. In the case above referred to, which came under my own care, freshly prepared mucilage of acacia together with tincture of opium proved of service, as was to be expected, in allaying the intestinal irritation.

Opium is also of great service in the attacks of colic which occur in chronic lead poisoning. The opium does not, as a rule, increase the constipation in such cases;

[1] Cf. Hugo Schulz, 'Arch. f. exper. Path. u. Pharm.,' 1884, Bd. xviii, S. 195.

nevertheless it is often advisable to give a mild laxative, such as castor oil, along with it. If the attacks of colic are very severe, recourse may be had to subcutaneous injections of morphia or inhalation of nitrite of amyl, and any other symptoms which may arise, must be met by their appropriate treatment.

I have already shown (see Vol. I, page 187) that there is a certain amount of truth in the assertion that the elimination of lead from the cells may be expedited by means of potassium iodide; but it is, I think, open to question whether its elimination can be promoted by using baths containing the alkaline sulphides. The latter are, no doubt, capable of precipitating lead as an insoluble sulphide from its solutions, but the skin does not seem to take part in the elimination of the metal from the system.[1] Potassium sulphide is sometimes prescribed in doses of 0·02 to 0·03 gramme ($\frac{1}{3}$ to $\frac{1}{2}$ a grain), made into pills with white bole and coated with silver or some other substances. These are taken two or three times daily; and in addition the patient is ordered a full length bath saturated with hydrogen sulphide, which is prepared by adding 30 grammes (about an ounce) of potassium sulphide, and eight grammes (two drachms) of sulphuric acid to the water in the bath, a little sulphur being also liberated in the process. In a bath of this kind, the skin will turn black if any particles of lead exist in the pores, for

$$K_2S_3 + 2H_2SO_4 = 2KHSO_4 + 2S + H_2S$$
$$H_2S + Pb = H_2 + PbS.$$

A metallic bath must not be employed for this purpose.

This antidote is of very doubtful efficacy, and, if there is no longer any lead in the stomach or intestines, may itself act as a poison if administered too freely. The sulphuretted hydrogen generated by the potassium sulphide is rapidly absorbed; it paralyses the central nerves and destroys the oxyhæmoglobin.[2] On this account it is necessary to exercise great caution when employing potassium sulphide externally, and still more when administering it internally.

[1] K. Miura, 'Berl. klin. Wochenschr.,' 1890, No. 44.

[2] Cf. A. Eulenberg, 'Schädl. u. gifhge Gase,' 1865, p. 260; also Hoppe-Seyler, 'Med.-chem. Untersuchungen,' 1866, i, p. 151.

Kalium Sulfuratum, liver of sulphur, or hepar sulphuris, is a brownish substance, the colour of which gradually changes to a yellowish green. It has a faint odour of sulphuretted hydrogen, deliquesces on exposure to the air, and is almost entirely soluble in two parts of water, forming an alkaline, yellowish-green, and somewhat turbid fluid. It is chiefly composed of potassium trisulphide, K_2S_3, with some thiosulphate, $K_2S_2O_3$, and sulphate, K_2SO_4. The two last salts are simply impurities resulting from the oxidation of the sulphide, and are of no importance therapeutically.

The following incident, which happened in Paris some years ago, shows how easily lead poisoning may arise, and from sources which are absolutely unsuspected. A baker had for some considerable time been in the habit of heating his oven with wood which was covered with paint, and which had been taken from houses lately pulled down. The heavy residue from the lead paint remained on the uneven surface of the oven, and so passed into his confectionery, and thence into the stomachs of his customers, about seventy of whom were taken ill, some of them suffering severely.[1]

Cases arising in a similarly unexpected way are constantly met with, and show how necessary it is for the physician, in diagnosing a disease and in searching after the cause which produced it, not to forget or neglect those symptoms which may be due to poison. Those who neglect to do this—and their number is not small—grope about in the dark to their own and their patients' injury. We shall meet with further striking illustrations of this when treating of mercury.

Except Argentum Foliatum, silver-leaf, which is used merely as a coating for pills, there is only one officinal preparation of silver, namely, Argentum Nitricum, nitrate of silver, or lunar caustic. It consists of white, sparkling, fusible rods, the fracture of which has a radiated crystalline

[1] Ducamp, ref. 'Centralbl. f. d. med. Wiss.,' 1878, p. 98.

appearance; it forms a clear, colourless solution with 0·6 parts of water, 10 parts of alcohol, and with ammonia. Its composition is $AgNO_3$. The aqueous solution has a neutral reaction, and gives on the addition of hydrochloric acid, a white flocculent precipitate of chloride of silver, AgCl, which is readily soluble in ammonia, but insoluble in nitric acid.

The alchemist Geber prepared nitrate of silver as early as the eighth century; in the eleventh Avicenna refers to the use of silver filing as a remedy.[1] A later author[2] scoffs at the Arabian physicians for expecting that a few grains of this metal, taken internally, should produce the same exhilarating effect upon the human heart as is felt by a man who possesses a satisfactory amount of it but does not swallow a single particle. Paracelsus (obiit 1541) extols the medicinal virtues of silver when dissolved in a distillate from nitre and vitriol, and taken internally. H. Cardanus (obiit 1576) and A. Paraeus (obiit 1590) employed lunar caustic dissolved in rose-water as a hair-dye. The use of this salt as a caustic came into vogue more and more from the seventeenth century onwards, and at the end of the eighteenth it was prescribed in England as an internal remedy for epilepsy, hysteria, and other nervous affections, in spite of the fact that Boerhaave (obiit 1738) had described it as a corrosive poison, which was on no account to be administered internally. In Germany, about 1798, Nord, then director of the "Narrenturm" at Vienna, was the first to experiment with it upon insane epileptics,[3] and since that time the use of the drug, though generally regarded with suspicion by scientific physicians, has never been entirely abandoned.

Let us in the first place discuss its employment externally. Its local action depends upon its power of precipitating albumen, and upon its caustic, astringent, and antiparasitic[4]

[1] L. Krahmer, 'Das Silber als Arzeneimittel betrachtet,' Halle, 1845, 355 pages.

[2] J. Hill, 'A History of the Materia Medica,' London, 1751, p. 28.

[3] 'Medicin. Nationalzeitung für Deutschland,' 1798, Supplement, S. 206 (quoted by Krahmer).

[4] Behring, "Der antiseptische Wert der Silberlösungen" 'Deutsche med. Wochenschrift,' 1887, No. 37.

properties, and the purposes for which it is employed are so various that it is only by clinical observation that you can become acquainted with them. Its effect upon the vessels was demonstrated by Rossbach.[1] It acts upon the exposed mesentery of the frog far more strongly even than the subacetate of lead. The constriction of the vessels takes place in from fifteen to fifty seconds after the application of the solution, and is the result of the direct local irritation, not of reflex action through the vascular centre. It may be so great as to reduce the vessels to half their normal width, and may be produced by a solution not stronger than 1 in 100. Inflamed vessels seem to react even more strongly. It is obvious that its direct effect in paralysing or destroying the emigrating white blood-corpuscles must also be useful.

The INTERNAL use of nitrate of silver has hitherto been altogether empirical, and derived from clinical experience; no toxicological investigations have yet thrown any light on the therapeutic facts.

It is in DISORDERS of the STOMACH and INTESTINE that the remedial action of nitrate of silver proves beneficial. The curative effects in cases of gastric disorder which are associated with or due to erosions, ulcers, or a relaxed condition of the mucous membrane is intelligible; the remedy acts upon them in the same way as it does upon the surface of external tissues or of mucous membranes, namely, as a gentle stimulant and astringent. If, on the contrary, there is no distinct lesion of the tissue, if, for example, we have to deal with a case of true gastric neuralgia, the effects of the remedy cannot be due to any mechanical change in the part, and therefore must probably result from some sedative action on the gastric nerves, but how this is brought about we are unable to explain. We are in the same position as regards its effect on acute and chronic DIARRHŒA. We do not know either the antecedent conditions, the nature, or cause of those particular forms of this disease which improve almost immediately upon the administration of even moderate doses of nitrate of silver; nor can we tell why in other

[1] Rossbach und Rosenstein, "Unters. über d. ört. Einw. der sog. Adstringentia auf die Gefässe," 'Pharmakol. Untersuchungen,' 1875, vol. ii, p. 78.

instances, apparently of the same nature, even large doses produce little or no effect. This is the reason why it is asserted that in cases of gastralgia and diarrhœa, no reliance can be placed on the drug.

I have already referred to its employment in EPILEPSY, for which it is still prescribed at the present time. Its use in this disease was particularly recommended by Romberg. If we judge merely from individual cases, there is hardly a malady in which results are so deceptive, simply for the reason that the number and intensity of the attacks not infrequently diminish without any treatment whatever. Nevertheless, judging from my own experience, and from trustworthy statements of others, it seems to me that there are cases of epielpsy in which improvement takes place only after a long course of treatment with nitrate of silver. Our want of knowledge as to the mode of origin of epileptic attacks precludes the possibility of any special indications being formulated for the use of this remedy.

In 1861 it was discovered accidentally by Wunderlich,[1] of Leipsig, that nitrate of silver sometimes has a beneficial effect in LOCOMOTOR ATAXY, tabes dorsalis. It happened in the following way:

A lady suffered from violent hysterical spasms, which were followed by paralysis. Nitrate of silver was the only drug which proved effective against this paralysis, and the patient in consequence took it so for so long a period as to develop the first signs of argyria—a condition which we shall presently consider. The results experimentally obtained in this case impressed Wunderlich with the conviction that nitrate of silver had a distinct therapeutic action, and he therefore tried it in some cases of progressive locomotor ataxy which were at the time under his care in the hospital wards. The result was better than he had anticipated. In a comparatively short time substantial improvement took place in seven cases, whilst confirmatory reports of the beneficial effects of the remedy were published almost simultaneously by Charcot, Vulpian[2] and others.

[1] Wunderlich, 'Arch. der Heilkunde,' 1861, vol. ii, p. 193, and 1863, vol. iv, p. 43.

[2] Vulpian, "Sur l'emploi du nitrat d'argent dans le traitement de

In his second publication on the use of nitrate of silver in incipient tabes dorsalis, Wunderlich says: "I can fully understand the distrust which meets the recommendation of a drug, of whose action, either physically or chemically, in a malady regarded as practically incurable, no explanation can be offered. But the very hopelessness of any other method of treating this disease, invites us to try a remedy which, at the worst, involves no danger; while anyone who realises the pain and misery which accompany this form of spinal paralysis, and which may possibly last for years, must be glad to know of a new remedy, even though it may not be useful in every case, and even though complete recovery may not take place. In this disease any considerable alleviation of suffering, and any restoration of power even though slight, is an inestimable benefit."

Subsequent reports as to the efficacy of the remedy have often been less favourable. Wunderlich's answer to an opponent is perhaps appropriate to many a failure: "It is only when a case has been fully reported in all its details that we can determine whether it is of any value as evidence; after the mere assertion that the remedy failed, it is at least doubtful whether the two cases were altogether suitable for this treatment, nor are we told in what way and with what result the treatment was carried out. Moreover K. adds that, encouraged by my results, he has used this remedy for paralysis of the sphincter ani in aged persons, and by means of it has put a stop to the troublesome involuntary evacuations which neither tonics nor opiates had been able to check for any length of time."

Leyden expresses a very guarded opinion as to the value of the remedy.[1]

There is one drawback to the use of nitrate of silver for any lengthened period, about which we possess more precise information than we do about its curative action. This is the production of a dark-grey or violet discoloration of the skin, termed argyria or argyriasis, which generally begins in the face, and is most distinctly marked there. It is per-

de l'ataxie locomotrice," 'Bull. gén. de thérap.,' 1862, vol. lxii, pp. 481 and 529.

[1] Leyden, 'Klinik der Rückenmarkskrankheiten,' 1875, Bd. ii, S. 358.

manent, and gives the person affected a negro-like appearance. When nitrate of silver was first introduced, the occasional occurrence of this discoloration was regarded somewhat in the light of a freak of nature. Among others Fourcroy,[1] writing from Paris in 1791, gives an account of such a case. Through Swediaur he had heard of a patient from the neighbourhood of Hamburg, who had become almost black (presque entièrement noir). He was a military chaplain in Stralsund, Willich by name, who had taken some of the secret remedies of the local physician Weigel, which contained a preparation of silver. It was only in 1817 that the subject was scientifically investigated by J. Albers,[2] and numerous exhaustive reports upon it have since been published.[3]

To produce this discoloration, the silver must be taken for several months, and to the amount altogether of from 15 to 20 grammes (from 225 to 300 grains). In one case argyria of the face was developed in a woman from taking a pill containing 0·02 gramme ($\frac{3}{10}$ of a grain) of nitrate of silver daily for two years, to restrain diarrhœa,[4] to which she had a tendency.

Disuse of the remedy from time to time does not prevent the development of the discoloration. From the time of its first appearance it steadily increases, even if the administration of the silver is discontinued, the change being completed by that portion of the metal which has accumulated in the organism.

The discoloration may affect all the organs. It consists partly of a collection of extremely minute granules, partly of a uniform brown staining of the tissues, by the silver. The tissues chiefly affected are the glomeruli of the kidneys, the plexus choroidei of the brain, the tunica intima of the aorta,

[1] Fourcroy, 'La méd. éclairée p. l. sciences physiques,' 1791, vol. i, p. 342.

[2] J. A. Albers, 'Arch. f. d. Physiol.,' 1817, Bd. iii, S. 572.

[3] C. Fromann, 'Arch. f. pathol. Anat.,' 1859, Bd. xvii, S. 146; Huet, 'Journ. de l'anat. et physiol.,' 1873, vol. ix, p. 408; B. Riemer, 'Arch. d. Heilkunde,' 1875, Bd. xvi, Ss. 296 und 385; Fragstein, 'Berl. klin. Wochensch.,' 1877, Ss. 209 und 294; A. Weichselbaum, ref. 'Centralb. f. d. med. Wiss.,' 1878, S. 954; P. Dittrich, ibid., 1885, S. 205.

[4] Schallenberger, 'Amer. Med. News,' 1887, p. 417.

the lymphatic glands of the mesentery, and the skin. In the last the pigment is chiefly deposited in the connective tissue of the cutis vera lying immediately below the epithelium, and in the sweat and sebaceous glands. The internal organs and tissues may be already distinctly affected by the silver at the time that the outer skin is only beginning to show traces of the discoloration.

The granular pigment consists of metallic silver in a state of minute subdivision, and has a slate-grey appearance. It is a result of the reduction either of the nitrate of silver—$Ag\ NO_3$—or of the chloride—$AgCl$—formed in the stomach, to the metallic state, and this reduction is completed by the cells of the organism. The part of the skin first affected is that which is most exposed to the light, namely the face. This discoloration has been attributed to the well-known property which silver solutions have of turning black. Pure nitrate of silver undergoes no change on exposure to light and air, but if in a solution any organic substance be present the solution first turns violet, and then gradually black flakes of minutely divided silver are precipitated. According to another view, the pigment which stains the skin is not metallic silver, but an *organic* compound of this base, which is insoluble in nitric acid but readily soluble in potassium cyanide.[1]

In a patient whose eyes had been treated for months with applications of nitrate of silver, the conjunctiva became dark brown, almost black. On examining an excised portion, Virchow[2] found that the silver had been absorbed into its substance, the whole upper surface of the connective tissue being tinted pale brown, but in the deeper layers the deposit had only taken place in the fine elastic fibres or corpuscles. The intercellular substance remained entirely unaffected. According to some authorities the formation of the pigment takes place in the intestine. The granules of silver are then mechanically distributed through the agency of the lymph and blood, and are frequently pressed through the vascular walls.

[1] St. Krysinski, 'Ueber den heutigen Stand der Argyriefrage,' Doctordissertation, Dorpat, 1886.

[2] R. Virchow, 'Cellularpathologie,' 1871, p. 250.

Against this view it may be urged that no other pigment is distributed from the bowel in the manner above described. Moreover, silver was found by O. Loew[1] inside the endothelial cells investing the Malpighian glomeruli, and not as a coating to the walls of the capillary tufts. Neither the vas afferens nor the vas deferens exhibited a trace of silver, nor was there any in the Malpighian capsules. This disproves the theory that granules of silver pass through the walls of the glomeruli; the probability is that the silver penetrates them in some soluble form, and is precipitated only after it has reached the cells. It appears that the reduction of the silver salts is effected by the living protoplasm. The kidneys of Batrachiæ placed in a slightly alkaline solution of silver become saturated with reduced silver, but only when the organs are in a living state. If they are subjected to the action of steam for a very short period, or to the vapour of ether or chloroform for a longer time, the reduction is no longer effected. In the protoplasm of *Alga syprogyra* the reduction takes place very rapidly; the oxygen of the silver salt combines with the living albumen, and the metallic silver is deposited in the cells. After introducing nitrate of silver into the stomachs of rabbits for several weeks, J. Jacobi found the epithelium of the intestinal canal free from colouring matter, while, on the other hand, the tissue under the epithelium was permeated by a finely granulated deposit.[2]

Two cases, in which argyria was developed by painting the throat and gums for some considerable time with a solution of nitrate of silver, possess some practical interest.[3] The discoloration was most marked in those parts to which the silver had been directly applied, but the skin, more particularly that of the face, was also affected.

Nitrate of silver is, in the stomach, partly converted into chloride of silver. In this state it cannot be absorbed, but in the presence of sodium chloride and of albuminous material it is soluble, and can consequently in this way be absorbed into the system. The excess of albumen in the

[1] T. O. Loew, 'Arch. f. d. ges. Phys.,' 1884, Bd. xxxiv, S. 602.

[2] J. Jacobi, 'Arch. f. exper. Path. u. Pharmak.,' 1878, vol. viii, p. 205.

[3] Duguet, 'Gaz. med. de Paris,' 1874, p. 351.

stomach leads to the formation of more albuminate than chloride of silver. The albuminate is also soluble in sodium chloride, and in an excess of albumen.[1]

Acute poisoning from nitrate of silver may arise from the introduction of small portions of it, or of strong solutions, into the stomach. Violent gastric irritation is produced, and the chloride and albuminate of silver which have been formed are vomited, together with the free residue. The vomiting should be promoted mechanically, by administering a dilute solution of salt in water, or milk, or whipped white of egg. A large dose of nitrate of silver is rarely absorbed into the system on account of the vomiting which immediately follows its exhibition. On this account, the only symptoms we shall probably have to treat will be those resulting from the irritant effect of the caustic, and this, owing to the rapid formation of chloride of silver, albuminate of silver, and nitric acid, where the stomach is NOT EMPTY, is usually slight.

The following case of chronic poisoning by nitrate of silver has been reported.[2] A gentlemen, sixty-one years of age, suffered from greyish-blue discoloration of the cheeks and mucous membrane of the nose and throat, accompanied by exhaustion, dizziness, loss of memory, pain at the back of the head, slight deafness with tinnitus aurium, weak eyesight, and chronic gastric catarrh. A closer examination disclosed tenseness of the cervical muscles, cramp of some of the ocular muscles, and bronchial catarrh. The patient had for years been in the habit of dyeing his beard with a strong solution of nitrate of silver. On discontinuing this, by the advice of his physician, all the symptoms, with the exception of the pigmentation of the tissues, rapidly disappeared.

After preparations of silver have been administered to animals for a considerable period in their food, general disturbance of the functions of nutrition is developed, together with loss of appetite, hyperæmia of the lungs, swelling and fatty degeneration of the cells of the liver and

[1] Bogoslowsky, 'Arch. f. path. Anat.,' 1869, vol. xlvi, p. 414.

[2] Bresgen, 'Berl. klin. Wochenschr.,' 1872, S. 72.

kidneys, fatty degeneration of the heart and muscles, a noticeable diminution of animal heat and of tissue change.[1]

Part of the silver absorbed is excreted by the intestines, even when it has not been taken by the mouth. The fæces are often dark in colour owing to the sulphide of silver formed in the intestines. A small quantity of the silver is also excreted by the kidneys.

If nitrate of silver is administered in the form of pills, the largest single dose being 0·03 gramme (under ½ a grain), it should only be given mixed with argilla, because when combined with organic substances it is very quickly converted into chloride of silver and then reduced to the metallic form. (ARGILLA, also called BOLUS ALBA,[2] is essentially silicate of alumina,—$Al_2Si_2O_7 + 2H_2O$,—with some other immaterial bodies. It is a white, friable, decolourising substance, somewhat sticky when moistened, disintegrating but insoluble in water.) Glycerine is the only substance which should be used to disguise the unpleasant metallic taste of nitrate of silver when given in solution. Even if we assume that chloride of silver is immediately formed in the stomach—

$$AgNO_3 + HCl = HNO_3 + AgCl—$$

it is not desirable to give the remedy in this form, as when already precipitated it is probably less soluble in solutions of sodium chloride or of albumen.

The following solution is one adapted for subcutaneous injection: 0·05 gramme (¾ of a grain) of freshly precipitated and well washed chloride of silver dissolved with 0·3 gramme (4½ grains) of sodium hyposulphite in 10·0 grammes (150 grains) of water. This must be preserved in a brown bottle. One c.cm. (15 drops) to be injected once or twice daily. It must be borne in mind that, with few exceptions, remedies are more energetic in their action when applied hypodermically than when otherwise administered. The above solution will keep almost unchanged for some weeks. Silver sulphide, however, is precipitated after a time.

As a milder caustic, ARGENTUM NITRICUM CUM KALIO NITRICO,

[1] On the subject of the poisonous effects of silver I would refer the reader to C. Gaehtgen's 'Die Wirkungen des Silbers auf die Atmung und den Kreislauf,' Giessen, 1890, Universtäts-Programm.

[2] From ἡ βῶλος = clod.

silver nitrate mixed with potassium nitrate, is officinal in Germany. It consists of one part of silver nitrate and two of potassium nitrate, and after being melted and poured into proper moulds it appears in the form of hard, greyish-white rods, and has a vitreous rather than a crystalline fracture.

Gold is still officinal in Germany in the form of AURO-NATRIUM CHLORATUM, sodium chloro-aurate. This is a golden yellow powder, completely soluble in two parts of water, but only partially soluble in alcohol. When fused it is decomposed, the gold being liberated. When chemically pure its composition is $AuCl_3 + NaCl + 2H_2O$. In the officinal preparation some sodium chloride is added, to render it less deliquescent, but the compound must contain at least 30 per cent. of gold.

The value of gold has been very variously estimated. While Pliny,[1] on the one hand, says that its discovery was the ruin of mankind, Christopher Columbus on the other, in his speech before their Spanish Majesties, wherein he referred to the abundance of it to be found in yet undiscovered lands, praised it as the most excellent thing in the world, capable of all things, even of the deliverance of souls from purgatory and their admission to Paradise.

Similar powers were also assigned to it medicinally for a certain period. I will only refer the testimony which Paracelsus gave in its favour. In his book 'Vom langen leben,' he says that of all elixirs, gold is the first and most potent. He refers to Aurum potabile or Tinctura auri, which is substantially a solution of gold in aqua regia and alcohol with the addition of an ethereal oil.[2] It is useful, he says, in every possible disorder; it renews and invigorates the body, and is potent against the evil influence of stars. As late as 1678 there appeared in Leipzig a monograph by P. J. Faber, 'De medicina universali sive auro potabili vero.'

Those who in later times held gold in high esteem as an internal remedy confined themselves to a few tangible points. Scrofula, syphilis, and dropsy were often treated with gold chloride during the first three decades of the present century.

[1] Pliny, 'Hist. nat.,' lib. 33, cap. 3.

[2] 'Pharmacopœa universalis,' 1838, vol. i, p. 343.

The chief representative of this practice was J. A. Chrestien, a physician in France, who in 1811 published a monograph in praise of it. This was received with no great favour, and during the scepticism prevailing in the "forties," it was hardly necessary to protest against the employment of gold.

For a long time after no notice of it was taken as a remedy, except as being an expensive caustic for cancer, &c. In recent times it has been used again in hysteria (Niemeyer), in chronic oöphoritis (Nöggerath) chronic metritis (L. Martini), chlorosis and paralysis (Burg), and spastic spinal paralysis (Kussmaul). The laudation of the elder Chrestien has been revived in our own day.[1] The internal use of chloride of gold, continued for some time, is said to excite ptyalism, but no stomatitis, such as is caused by quicksilver.

The critical investigation of the statements above referred to is a matter for clinical observation. I will here only briefly discuss the results of some experiments which have been made on animals. No light has been thrown by these experiments on any point in therapeutics. Aronowitsch, in his experiments on frogs with diluted non-caustic solutions of auro-natrium chloratum and with solutions of the neutral double salt, sodio-aurous thiosulphate, found that they produced paralysis of the nerve centres; and in similar experiments on rabbits, the doses being gradually increased, they caused catarrh and general paralysis, while one large single dose (0·3 to 0·5 gramme) of the latter salt produced great restlessness, rapid pulse, and diarrhœa. Recovery followed in from three to four hours. Finally, when 1 gramme was subcutaneously injected, death ensued within an hour from paralysis of the respiratory organs, accompanied with convulsions and œdema of the lungs.[2]

Similar observations to the above were also made by Orfila.

[1] A. T. Chrestien, 'De l'efficacité de l'Or et de ses diverses préparations contre la Syphilis et la Scrofule,' Montpellier, 1870, pp. 8—26.

[2] Aronowitsch, 'Doctordissertation,' Würzburg, 1881.

XXI.

The preparations of mercury—Employment of metallic mercury in intestinal obstruction—Blue ointment—Its mode of action—Solubility of mercury in organised tissues—The sulphides of mercury—The oxides—The chlorides and iodides—The cyanide—Maximum dose of each preparation—Poisonous effects—Experiments on animals—Analysis of the results—Elimination of mercury from the system—Detection of its presence by electrolysis—Guaiacum, sarsaparilla, &c.

Mercury, the preparations of which even at the present day are very numerous, is pharmacologically by far the most important of the noble metals.

There are three points of view from which these preparations may be considered,—either according to their so-called physiological effects on the animal body, or according to the results obtained clinically, or we may take each preparation in detail. The first of these is as yet of little importance, for the action of mercurials upon the healthy body is not characteristic, neither does it afford any explanation of the therapeutic effects; the second would take us further than is necessary into the clinical province; the third plan is the only one by which on a pharmacodynamical basis the action of these remedies can be discussed both theoretically and practically.

Pure metallic mercury is officinal, and it is sometimes used in a special way. A single dose of from 100 to 200 grammes (3 to 7 ounces) or more is poured down the throats of patients suffering from intestinal obstruction due either to invagination, twisting, or paralysis of the bowel, or to fæcal accumulation, or to a mass of ascarides. The above dose, owing to the high specific gravity of the metal, dose

not exceed more than one or two liqueur glasses full. This concentrated heavy mass is supposed to find its way to the spot where the obstruction exists, and then by direct pressure to overcome it, or else, by reflex stimulation from some distant spot, to develop peristaltic movement of the inactive bowel. The first was the view formerly held; the last originated, so far as I can ascertain, with Traube.[1]

At the present time the use of metallic mercury for this purpose has almost been given up. It is a somewhat violent proceeding, as there may be some doubt as to the cause of the obstruction, and as to the amount of danger it involves.

There is the possibility of causing rupture of the bowel; of some portion of the metal being volatilised in the bowel; and finally, it is impossible in those cases where beneficial effects have followed its use to say that these were due to the remedy, and not to the ordinary course of the disorder.

In a paper on intestinal obstruction by K. Bettelheim[2] reference is made to seventy cases which were treated with metallic mercury, and which were recorded in the journals during the last forty years.

Of these seventy cases, fifty-seven recovered and thirteen died. Three of them were successfully treated by the author of the paper, who came to this conclusion, that practical experience showed that metallic mercury was not a useless remedy, but was often of great service in cases of intestinal obstruction which would be otherwise incurable, and that no unpleasant symptoms, such as rupture of the bowel, followed the administration of the remedy.

The further investigation of the matter must be left to clinical observation. Traube's statements, however, are interesting pharmacologically. Four doses of metallic mercury, amounting altogether to one kilogramme (nearly two and a half pounds), were given within eighteen hours, and apparently, so far as the symptoms were concerned, with good results, for the vomiting ceased and the bowels were relieved. The malady, however, was incurable, and the patient died.

[1] Traube, 'Beiträge zur Pathologie,' u. s. w., 1871, Bd. ii, S. 354.

[2] K. Bettelheim, "Mercurius vivus bei Darmstenosen," 'Arch. f. klin. Med.,' 1882, Bd. xxxii, S. 53.

On post-mortem examination four fifths (800 grammes) of the amount administered were found located in the FUNDUS VENTRICULI. On this Traube remarks, "If the spot to which the quicksilver has passed, and where it lies in any considerable amount, is at some distance from the part where the obstruction exists, then, owing to its weight, the quicksilver will cause great distension of the loaded part, and, consequently, considerable stretching both of the part itself and of the centripetal nerve-fibres distributed to it. The effect of this unusually strong stimulation of the nerve-fibres would call forth an unusually powerful contraction of the muscular fibres, which would be propagated along the intestine up to the point where the obstruction exists, and this contraction, so long as the stretched nerves retain their irritability, and are continuously stimulated, must constantly recur. If, moreover, it is true that the peristaltic movements of the bowels may originate in the stomach, then the quicksilver resting in the fundus of that organ may in this way be useful."

It has also been assumed that from metallic mercury, a certain amount of some soluble compound may be produced in the alimentary canal, which, if absorbed to any extent, would produce poisonous effects.

The occurrence of such a result, though certainly not improbable, is contrary to clinical experience;[1] and in experiments on animals nothing of the kind has been observed. Ausonius the poet (obiit A.D. 395) describes[2] how an unchaste woman endeavoured to poison her husband. As the attempt failed, she gave him a large dose of quicksilver. This, however, proved to be an antidote, for it acted on the bowels, and thereby eliminated the poison previously administered. Rhazes, the distinguished Arabian physician and writer, who died at Bagdad A.D. 930, mentions that he poured a considerable quantity of the metal into a monkey's stomach, and that this produced no bad effects; he states, nevertheless, that the preparations of mercury are poisonous. C. Hoffmann gave a small cat and two

[1] Bettelheim, loc. cit., S. 59.

[2] Ausonius, Epigramma x:—"Toxica zelo typo dedit uxor mœcha marito . . . ."

young rabbits each 7·2 grammes (108 grains), and repeated the dose eight times, at intervals of from one to two hours, but no trace of quicksilver was afterwards to be found, either chemically or microscopically, in the intestinal glands, in the chyle, the portal vein, the liver, the bile, the kidneys, or the urine.[1] We need not, therefore, under ordinary conditions, attach any importance to the statement of Dioscorides (lib. v, ch. 110), that "hydrargyrum vim habet perniciosam, dum voratur, suo enim pondere interna perrodit;" for which he recommends all kinds of potions and subsequent vomiting, but more particularly the administration of gold dust, which he asserts is a "wonderful" remedy.

Unguentum Hydrargyri Cinereum, blue ointment, is the first and simplest of the mercurial preparations. It is a bluish-grey ointment, in which no small globules of mercury can be seen with the naked eye, and is prepared by rubbing intimately together 13 parts of lard with 7 of suet and 10 parts of mercury.[2]

The name Unguentum Neapolitanum given to this ointment, arose from the fact that when syphilis was first introduced into Europe, a severe epidemic occurred in the district around Naples, and this ointment was there used as the remedy.[3] Columbus had returned to Europe with his vessels in the spring of 1493, and among the other gifts which his companions brought home from the newly discovered territory, syphilis was included. (Smallpox, previously unknown in America, was introduced there from this continent.) This disease was confined at first to the southern parts of Spain, but two years later was conveyed to Italy by the troops which the king of Spain sent to help the king of Sicily against the French, who were besieging Naples. The Spaniards, in accordance with the warlike customs of

[1] Kussmaul's monograph, 1861, S. 41.

[2] [The British Pharmacopœia directs that this should be prepared by rubbing together 16 parts each of mercury and lard and 1 part of suet, until metallic globules cease to be visible.—Transl.]

[3] Ch. Girtanner, 'Die venerische Krankheit.,' 1788, Bd. i, S. 44; C. Binz, "Die Einschleppung der Syphilis in Europa," 'Deutsch. med. Wochenschr.,' 1893, No. 44.

the time, ravished the women of the Campania, and infected them, and they in their turn infected the French. The latter were compelled to retire, and spread the disease all along their route through Italy, and afterwards north of the Alps. The French called the new disorder Mal de Naples, because they had contracted it when before Naples. The Italians named it Mal Francese, because the French had distributed it along the whole peninsula; physicians in other countries named it Morbus Gallicus, as it spread chiefly from France to all other parts; and as the symptoms with which it commenced were peculiar and previously unknown, it was also termed Morbus novus.

Syphilis, having been long endemic in America, existed there only in a mild form. When introduced into Europe, where the surroundings of the people were dirty and their habits dissolute, it fell upon a new soil; for the gonorrhœal virus, with the ordinary effects of which, as well as with the numerous complications arising therefrom, the Jews, Greeks, and Romans were very familiar, is, as is well known, something totally different, and possesses nothing in common with syphilis except the way in which it is propagated. The disorder spread like a spark of fire applied to dry wood, especially in Germany—according to Ulrich von Hutten's account—because the drinking habits of the people rendered them more susceptible to its action.[1]

Quicksilver rubbed together with fat and various other substances, had been employed long before in diseases of the skin; after the appearance of syphilis its use became more general. We find the ointment described at the end of the fifteenth century by several writers, who approve of its use, and refer to the increased flow of saliva thereby induced. It met with great opposition and was frightfully misused,

[1] Albert Dürer wrote in 1506 from Venice to W. Pirckheimer, "Ask our Prior to pray for me that I may be preserved, and more particularly saved from the French disorder; I do not think that at present I am afraid of anything more dreadful, for simply every one has it." A few years later Paracelsus writes in his 'Fragmenta Medica,' "I therefore purpose first to write about the French disorder, as it is one of the most common diseases, affecting princes, nobles, rich and poor, high and low, in Germany, France, and other foreign countries."

but it has maintained its position as a valuable remedy to the present time, and a long series of clinical observations recently conducted at the hospital at Würzburg have demonstrated the fact that it is superior to all other remedies in preventing a return of the disease.[1] How are its effects produced? Is the mercury, when applied in this way, absorbed by the skin, and does it pass thence into the circulation? And in what form does the mercury exist in the blue ointment?

When recently prepared, the blue ointment is a mixture of fat and metallic mercury, the small globules of which can be distinctly seen under the microscope with a low power. After a time these are converted gradually into the oleate of mercury, the ointment acquires an acid reaction due to free oleic acid, and if boiled with ether, and the solution filtered and evaporated down, the residue will, after being decomposed with potassium chlorate and hydrochloric acid, invariably yield a copious precipitate when treated with sulphuretted hydrogen.[2] Neither the metal nor its oxide is soluble in ether; it is, however, readily soluble when combined with a fatty acid. In the ointment, therefore, this compound has been formed, and it is owing to the presence of this compound in ointment which has been made some time, that the addition of a small portion of the latter greatly facilitates the intimate mixture of the metal with fat, when preparing a fresh supply. The mercurous compound forms a fine coating over the minute globules, which keeps them separate and facilitates the intimate mixture of the metal with the fat. The preparation of the ointment is also facilitated—as every druggist knows—by the addition of a small quantity of ozonised turpentine. The nascent oxygen combines with the metal with the same results as those above described.

The question whether the compound contains mercurous or mercuric oxide has been differently answered. Doubtless both would be present in proportions varying with the age

[1] E. Lexer, 'Arch. f. Dermat. u. Syph.,' 1889, Bd. xxi, S. 715.

[2] K. Voit, 'Physiologisch-chemische Untersuchungen,' Augsburg, 1857, S. 91.

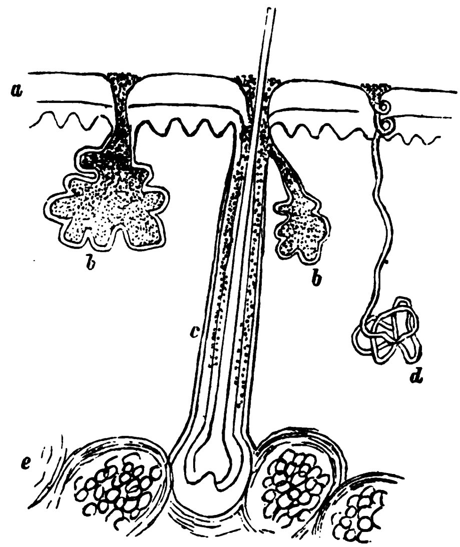
of the preparation; it cannot be assumed that the whole of the mercury is oxidised in the ointment, as, however long the latter has been kept, after dissolving the fat in alcohol, a considerable proportion of the metallic mercury is left behind. In the ointment, therefore, the metal exists in a finely divided state, as well as in the form of mercurous and mercuric oxides.

Both the metal and the mercurous compound with the fatty acid, when rubbed into the skin, are absorbed and pass into the circulation. Numerous investigations[1] have been made with regard to this.

Isidore Neumann and Fürbringer, from experiments on rabbits and on human beings, arrived at the following results. The globules of mercury, as well as its oleate, on being rubbed into the skin pass into the hair-follicles as far as the bulbs; they also pass into the sebaceous follicles which open on the surface, as well as into those which open into the hair-follicles,—into the former to a larger extent than into the latter. The orifices of the sweat-glands frequently contain a considerable number of these globules; in the sweat canals they are rarely seen, and are never found in the glands themselves. The globules are absorbed from these parts, for in a few days they are coated with oxide and diminished in number, and in a few weeks they entirely disappear. In the internal organs the presence of mercurial compounds can be detected chemically, but no globules are ever found there. The absorption distinctly takes place from the parts which have been rubbed, for I have detected the presence of mercury inside the body when its entrance through the respiratory organs had been completely pre-

[1] For full details the reader may be referred to the following authorities:—Kletzinsky, 'Heller's Arch. f. path. u. phys. Chem. u. Mikrosk.,' 1852, S. 291; v. Bärensprung, 'Ann. d. Charité zu Berlin,' 1856, Heft 2, S. 110, und 'Journ. für prakt. Chemie,' 1850, Bd. l, S. 21; G. Lewald, loc. cit., 1857, S. 25; K. Voit, loc. cit., 1857, S. 51; R. Overbeck, 'Mercur und Syphilis,' Berlin, 1861, S. 17 u. 64; Rindfleisch, 'Archiv f. Dermatol.,' 1870, Bd. iii, S. 309; Auspitz, 'Wien. med. Jahrb.,' 1871, S. 316; J. Neumann, 'Wien. med. Wochenschr.,' 1871, S. 1209; P. Fürbringer, 'Arch. f. pathol. Anat.,' 1880, Bd. lxxxii, S. [illegible]

vented. The globules are not absorbed by inunction through the uninjured epidermis and cutis vera.



The passage of mercurial globules into the cutaneous follicles. (After I. Neumann and P. Fürbringer.)

a. Epidermis. *b*. Sebaceous follicles. *c*. Hair-follicles. *d*. Sweat-gland. *e*. Subcutaneous fatty tissue.

After inunction with the ointment, sufficient mercury can be volatilised from the parts to promote a curative effect in syphilitic disorders, and also to set up very rapidly inflammation of the mouth and salivation, either in the patient himself or in his attendants. In such cases we see the direct action of the remedy, the rapidity and intensity of which will naturally vary according to circumstances, and will be especially influenced by the temperature of the room and the state of the patient's mouth. The higher the temperature the more rapidly will the mercury be volatilised, and if the mouth is in an unhealthy state, the more rapidly will its mucous membrane be affected. Rabbits which were shut up in a warm room, and exposed to the emanations

from mercurial ointment, died from stomatitis and marked enlargement of the salivary glands.[1]

The absorption from the cutaneous follicles of the metal in this state of minute subdivision and of its compounds with the fatty acids, insoluble though they are in the fluids of the animal economy, is effected by the action of the sodium chloride, the volatile fatty acids, the albumen, and by the glandular secretions.

Mialhe discovered that when metallic mercury or one of its officinal preparations was agitated with a solution of 6 parts of sodium chloride, 6 of ammonium chloride, and 10 of water, air being present, there was always a certain amount of mercuric chloride formed, even at the ordinary temperature of the atmosphere.[2] Lewald reduced chemically pure metallic mercury to a state of minute subdivision by agitating it with water and urea. He then mixed it with ammonium butyrate, and allowed it to stand exposed to the air for twelve hours. The solution, after filtration, gave a black precipitate of mercuric sulphide when treated with hydrogen sulphide. A soluble compound, therefore, of the mercury had been formed by the ammonium butyrate. The same result was produced by mixing the finely divided mercury, resulting from its agitation with water and urea, with a saturated solution of sodium chloride to which two parts of water had been added, and allowing it to stand exposed to the air for twelve hours. A certain amount of the soluble mercuric chloride was thereby formed.

This is, therefore, the explanation of the way in which the minute globules of mercury or its compounds with the fatty acids are absorbed from the cutaneous follicles. The metal being converted either into an oxide or a chloride, is rendered soluble in the aqueous portion of the lymph or blood, and so passes into the circulation. It causes neither coagulation nor precipitation in the vessels, the small

[1] G. Kirchgässer, 'Arch. f. pathol. Anat.,' 1865, Bd. xxxii, S. 145; J. Samelsohn, 'Berl. klin. Wochenschr.,' 1872, S. 636; Fr. Müller, in Gerhardt und Müller, 'Mitteil. a. d. med. Klinik,' 1886, ii, S. 355; Gerhardt, 'Deutsch. med. Wochenschr.,' 1894, Beitrag No. 10, S. 75.

[2] Mialhe, 'Ann. de Chim. et de Phys.,' 1842, vol. v, p. 169.

amount of mercury, probably in the form of an albuminate, being kept in solution by the sodium chloride contained in the fluids.

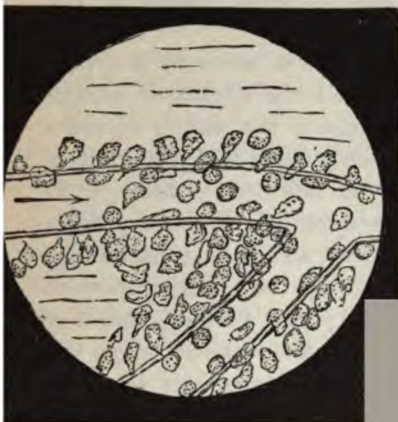
This view has been confirmed experimentally as follows:

An emulsion of mercury in an extreme state of subdivision, made with a very little mucilage and glycerine, was injected into the veins of certain animals, and apparently with no bad effects. After not less than twenty-four hours they were killed and the blood-serum tested for the presence of any soluble salt of mercury. On several occasions its presence was demonstrated. The metal, therefore, had been oxidised in the system. A watery extract of the liver contained a considerable amount. Numerous globules were also detected; the smaller ones were dull and distorted, black, and irregular in shape. On treating them with acetic or hydrochloric acid the irregularities disappeared, and the mercury again presented a glittering appearance. These changes were due to the intermediate formation of mercurous oxide.

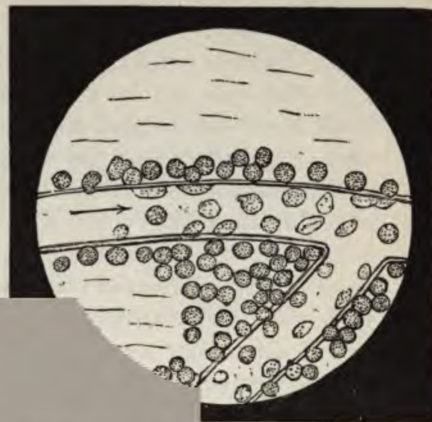
We will now consider the MODE OF ACTION of the remedy when, in acute inflammatory conditions, the blue ointment is rubbed into the surrounding parts. Its effect is practically to retard suppuration—that is the formation of an abscess from an abundant emigration of the colourless blood-corpuscles—and to prevent the earlier stages of inflammation from running on to the formation of an abscess.

I show you here (I), without depicting the stream of red blood-corpuscles, the suppurative process in the frog's mesentery, as described by W. Addison and Cohnheim. Suppuration is going on actively; the white blood-corpuscles have migrated in all directions through the thin capillary walls, they are loitering against the walls of the vessels and adherent to them. I now show you under the microscope the highly inflamed mesentery (II) of a frog to which five minutes ago I applied a few drops of a solution containing 0·01 per cent. of corrosive sublimate and 1 per cent. of sodium chloride. You see there that all the corpuscles which, owing to their special endowment and activity,[1]

[1] With regard to this see M. Lavdowsky, "Mikroscopische Unter-



I.—Normal suppuration.



II.—Suppuration modified by the action of mercury.

are about to migrate through the vascular wall, or have already done so, have been attacked and paralysed by the corrosive sublimate. The suppurative process has been arrested,[1] and has proceeded no further than the stage of hyperæmia with its accompanying phenomena.

There is no reason whatever to doubt that the same effect is frequently produced in the human subject, for the soluble preparations of mercury, in whatever way they are applied, exert the same paralysing effect on protoplasm as you here see under the microscope, and the suppurative process in man runs precisely the same course as in the frog. At the same time, other causes may contribute to the antiphlogistic action of the blue ointment; for instance, the mercury may possibly paralyse the active agent—if this is some bacterial organism—which produces the inflammation, or the gentle friction of the part may promote the contraction of the vessels and accelerate the stagnant circulation which results from the aggregation of

suchungen einiger Lebensvorgänge des Blutes," 'Arch. f. path. Anat.,' 1884, Bd. xcvii, S. 177.

[1] For a confirmation of the experiments as above described, see R. Heinz, 'Arch. f. path. Anat.,' 1889, Bd. cxii, S. 241.

the white corpuscles against the vascular walls of the inflamed spot.

No decisive explanation of the action of mercury in syphilitic affections can be suggested until the syphilitic poison itself has been isolated and subjected to the action of mercury, and the way in which its effects are afterwards modified under mercurial treatment has been noted. It is probable that the vitality of the syphilitic micro-organism is lowered by the action of mercury, and is in consequence more easily eliminated or destroyed by the curative powers with which the system is endowed; and further, mercury and iodine may act as specifics in the disease, since the micro-organism, or cause of the disease, is specially sensitive to the action of these remedies.

Reference must also be made to the poisonous action of the blue ointment on the larger parasites infesting the human skin. If my memory is correct, it was Hyrtl who devised an ingenious experiment in order to determine whether the animals were killed by the fat blocking up their tracheæ, or were poisoned by the mercury. He placed one pediculus pubis in some blue ointment, and another in ordinary fat. On removing them at the end of a few hours the former was found to be dead; the latter very quickly became quite lively.

Emplastrum Hydrargyri, mercurial plaster, is prepared from metallic mercury, which forms one fifth of the mass,[1] together with turpentine (the oleo-resin), lead plaster, and yellow wax. It is a thick, grey mass in which no globules can be detected by the naked eye. It promotes the cicatrisation of syphilitic ulcers and the absorption of tumours due to the same cause. From the almost invariable presence of nascent oxygen in the turpentine we may assume that some portion of the metallic mercury is thereby oxidised. The sodium chloride and other cutaneous secretions will probably act upon the plaster in the same way as they do on blue ointment. There is consequently no difficulty in accepting Röhrig's statement[2] that after applying a mercurial plaster the size of

[1] [The Emplastrum Hydrargyri (B. P.) contains one part of mercury in three of the plaster.—Transl.]

[2] Röhrig, 'Die Physiologie der Haut,' 1876, S. 108.

his hand for two days between the shoulders, and preventing any vaporisation of the mercury by coating the plaster thickly over with collodion, he was able to detect the presence of the metal in the urine.

HYDRARGYRUM OXYDATUM, mercuric oxide, HgO, is officinal in two forms, prepared respectively by the dry and the moist method. The former is obtained by heating mercuric nitrate, $Hg(NO_3)_2$, whereby two molecules of NO_2 and one atom of O are dissipated. It has an orange-red colour, is crystalline, and almost entirely insoluble in water. The other is prepared by precipitation from a solution of mercuric chloride by means of solution of soda—

$$HgCl_2 + 2NaOH = 2NaCl + H_2O + HgO.$$

It is a yellow amorphous powder, and is termed the yellow oxide of mercury. As is well known, both the red and the yellow oxide of mercury volatilise when heated, and are decomposed into oxygen and metallic mercury.[1]

The maximum dose of both these preparations is identical, 0·02 gramme (about $\frac{1}{3}$ of a grain), but they are no longer administered internally. On the other hand, the UNGUENTUM HYDRARGYRUM RUBRUM, which, made according to the British Pharmacopœia, contains 1 part of the red oxide in 7 of the ointment, is much employed externally. Oculists, however, prefer using the amorphous yellow oxide, because in the first place the red oxide, even after careful trituration, always presents some sharp crystalline points, which irritate the conjunctiva; and in the next, the amorphous yellow oxide being in a state of finer subdivision, is supposed to act more energetically. In Germany the ointment of the red oxide is alone officinal. [The British Pharmacopœia contains an oleate of mercury, Oleatum Hydrargyrum, which is pre-

[1] The conversion of quicksilver into the red oxide and the subsequent transformation of this into metallic mercury was regarded by the celebrated Gabriele Fallopia (obiit 1562) as a symbol of the resurrection. In his 'Tractatus de Morbo Gallico,' cap. 27, he writes as follows :—" Videtis argentum vivum converti in præcipitatum, in pulverem, tamen iterum potest in hydrargyrum reduci : videtur species resurrectionis, miraculum Dei reservatum. Hoc exemplo apud incredulos possumus confirmare, ut verbo Dei ex nostro cinere resurgamus."

pared by mixing 1 part of the yellow oxide of mercury with 9 parts of oleic acid.]

The most important preparations of mercury are its two chlorides. One of these is the Perchloride, $HgCl_2$, HYDRARGYRUM PERCHLORIDUM, also usually called CORROSIVE SUBLIMATE, or sometimes simply the sublimate. The characters of this, according to the Pharmacopœia, are white, transparent, glittering crystals, yielding, when triturated, a white powder. When heated in a test-tube it melts and sublimes. It dissolves in 16 parts of cold and 3 parts of boiling water, in 3 parts of alcohol, and 4 parts of ether. The aqueous solution has an acid reaction, which becomes neutral on the addition of sodium chloride.

Its name sublimate is derived from the way in which it is prepared, which is by heating together sodium chloride and mercuric sulphate, when double decomposition takes place, sodium sulphate is formed together with mercuric chloride, which sublimes:

$$HgSO_4 + 2\,NaCl = Na_2SO_4 + HgCl_2.$$

When crystallised from its solutions in alcohol or hydrochloric acid, it appears in the form of prismatic crystals.

Both egg albumen and serum albumen are precipitated from their solutions by mercuric chloride, the precipitate being soluble either in an excess of albumen or on the addition of sodium chloride. This explains why corrosive sublimate can be absorbed from the alimentary canal and by the lymphatics, without the formation of coagula, and also why sodium chloride is added to a solution of the perchloride, when this is to be employed hypodermically.[1] In what particular form it circulates through the vascular system has not as yet been accurately determined.

The action of corrosive sublimate on all the LOWEST FORMS[2] of animal and vegetable life is very striking. Numerous investigations have been made on this point, and the result has been, that mercuric chloride is now the substance most

[1] E. Stern, 'Berl. klin. Wochenschr.,' 1870, No. 35; M. Marle, 'Archiv für exper. Path. u. Pharmak.,' 1875, Bd. iii, S. 397.

[2] R. Koch, 'Mitteil. a. d. kaiserl. Gesundheitsamte,' 1881, Bd. i, S. 276.

generally employed for the purposes of disinfection and antisepsis. With reference to this, however, it is noteworthy that the sublimate, as well as other antizymotics whose action has been tested, if added in a sufficiently dilute form will, instead of destroying, intensify the activity of the yeast-cells in a very marked manner.[1]

There is another property of corrosive sublimate which is of considerable interest therapeutically, and resembles the action of arsenic, namely, that small and repeated doses increase the bodily weight both of healthy human beings and of animals.

It has frequently been observed that syphilitic patients, when judiciously treated with the perchloride of mercury, not only recover from the disease, but also increase in weight. This fact led Liègois to investigate the point. For two months he administered the sublimate, subcutaneously, to two rabbits, giving to each daily one milligramme ($\frac{1}{66}$ of a grain). At the end of this time the animals had increased in weight 650 and 1000 grammes respectively (about $1\frac{2}{5}$ lbs. and $2\frac{1}{2}$ lbs.). Another animal, which was pregnant, was treated in the same way. It brought forth at the full period six healthy young ones, and in addition gained 220 grammes (nearly $\frac{1}{2}$ lb.) in weight. To a fourth animal Liègois gave, daily, double the dose. It wasted away and died at the end of a month. These facts correspond with the gradual increase in weight which has been observed in patients suffering from chancre, who are being treated by the daily subcutaneous injection of 2 milligrammes ($\frac{1}{33}$ of a grain) of the perchloride. The increase of weight, in a few weeks, in these patients is very marked, when compared with the weight of those not treated with mercury. One patient to whom the perchloride was not administered lost 1100 grammes in weight, in the same time that another patient who was treated with the subcutaneous injections gained 1255 grammes in weight.[2] Similar results were subsequently observed by Hughes Bennett, of Edinburgh, when experimenting on dogs to determine the action of mercury on the biliary secretion. Twelve dogs which had large doses given

[1] Hugo Schulz, 'Arch. f. d. ges. Physiol.,' 1888, Bd. xlii, S. 517.

[2] Liègois, 'Gaz. des hôpitaux,' 1869, pp. 347 et 350.

to them, died; two which had small doses grew heavier and stronger.

A few years later Wilbouchewitsch[1] arrived at the following conclusions :—Mercury given in small doses to syphilitic patients for a certain period causes an increase in the number of the red blood-corpuscles, and a slight decrease in the number of the white; the number of both in the blood gradually becomes normal. If the treatment is continued for too long a period, or if the doses of mercury administered are too large, the contrary results are produced, together with diarrhœa, &c.

Keyes[2] experimented upon himself, upon a young man the subject of a soft chancre, and upon some syphilitic cases. Whilst perfectly well he took 0·012 gramme (less than $\frac{1}{5}$ of a grain) of the green iodide of mercury three times a day. The young man took daily, for four months, 0·06 gramme ($\frac{9}{10}$ of a grain) of the green iodide, and then gradually discontinued it. Both these persons felt quite well whilst taking the drug, the latter increased in weight, and in both the number of the red corpuscles increased. This also occurred—in fact, the number became larger than normal—in the syphilitic cases. Keyes considers that mercury acts as a "tonic" when given in small doses to healthy persons for a limited period.

H. Schlesinger's experiments[3] on warm-blooded animals produced a precisely similar result.

No explanation is offered by the writers above referred to as to how this increased weight is caused—whether the mercury impedes the normal disintegration of the red blood-corpuscles and the oxidation of the tissues, or whether, on the other hand, it acts as a gentle stimulant on the blood and fat forming processes. The latter is the more probable action. This is in harmony with the experiment to which I have already referred, namely, that in an extremely dilute solution of the sublimate (1 in 600,000) the activity of the

[1] Wilbouchewitsch, 'Arch. de Physiolog.,' 1874, vol. i, p. 509.

[2] E. L. Keyes, 'American Journ. of Med. Sciences,' 1876, vol. lxxi, p. 17.

[3] H. Schlesinger, 'Arch. f. exper. Pathol. u. Pharmak.,' 1881, Bd. xiii, S. 317.

ordinary yeast cells increased. The same effect may be produced on the cells in the animal organism.

The poisonous effects of the various preparations of mercury, including the perchloride, will have to be discussed later on. We will now consider another preparation, namely, the subchloride.

Hydrargyrum Chloratum, Hydrargyrum Subchloridum, mercurous chloride, HgCl, usually called calomel, is a yellowish-white powder, which, however, when magnified 100 times, appears distinctly crystalline. It is insoluble in water and alcohol. When heated it volatilises without liquefying. It is prepared by rubbing together four parts of mercuric chloride moistened with alcohol, and three parts of metallic mercury, and when dry, subliming in a suitable apparatus.

A distinction is to be drawn between this preparation and the Hydrargyrum Chloratum vapore paratum, which is a white powder, becoming yellowish when well triturated. The latter appears to be chiefly amorphous with a crystalline admixture, the crystals, however, being much smaller than those of the preceding compound. It is prepared by driving the vapour of calomel, by means of a current of hot air, into a receiver containing aqueous vapour. As it is in a state of finer subdivision it acts more rapidly and effectively than the other form of the subchloride.

Calomel came into general use in Europe in the sixteenth century, and was soon regarded as a remedy of the first importance. J. Caspar, in a treatise published at Tübingen in 1760, describes it as a "panacea," and by the end of the century there was hardly a physician who did not administer it systematically and extensively. It was regarded, especially in combination with opium, as a general antiphlogistic remedy for the treatment of inflammation, no matter what part was affected or what had been the cause giving rise to the disorder.

A reaction, however, gradually set in with regard to its use. On this point I will merely refer to a little work of Dr. A. Halliday,[1] of the Bengal Medical Service. In reply

[1] Waring, 'Bibliotheca Therapeutica,' London, the New Sydenham Society, p. 494.

to a circular issued in 1818 by the Bengal Medical Board, calling for information from the medical officers of the Presidency with regard to the diseases of the country, their treatment, &c., he sent in a report, the sum and substance of which is embodied in the following table :

	Cases treated.	Grains of calomel to each patient.	Proportion of deaths to cases.
From 1st May, 1816, to 30th April, 1817	1063	$102\frac{8}{9}$	1 in $8\frac{3}{4}$
,, 1817 ,, 1818	875	208	1 in $7\frac{1}{2}$
,, 1818 ,, 1819	2089	$51\frac{1}{10}$	1 in 15
,, 1819, to 17th Aug., 1819	635	$28\frac{1}{2}$	1 in 20
,, 1819, ,, 21st Jan., 1820	707	$123\frac{3}{4}$	1 in $6\frac{1}{5}$

The report gave great offence to the ruling powers, who removed the audacious writer, on account of his "rash and crude innovations," from the situation of Presidency Surgeon. He, however, memorialised the Court of Directors,[1] the result being that he was reinstated in the service.

Opposition to the misuse of this alleged "cure-all" was subsequently further developed and intensified. The result was, that the remedy in the middle of the present century was placed on the proscribed list, owing to the sceptical bias which then dominated the teaching of scientific medicine. At the present day, however, an unprejudiced view has been formed as to its therapeutic effects, and it is now held that its use is beneficial in syphilis when carefully administered; that it is of service in the early stagès of typhoid fever and in certain forms of intestinal catarrh; and that it is useful as a laxative, and as a diuretic. Although these indications for its use appear to be so diverse, they may be referred to one uniform basis.

In the first place, by what means is the insoluble calomel dissolved by the animal fluids? That it is dissolved is clear from the fact that mercurial stomatitis can be rapidly produced by the administration of calomel pills.

In 1765 Proust[2] proved that the alkaline chlorides trans-

[1] A. Halliday, 'Memorial to the Honorable the Court of Directors for the Affairs of the East Indian Company,' Calcutta, 1820.

[2] Proust, see Mialhe, loc. cit., p. 171.

form the subchloride of mercury or calomel into the perchloride, and Mialhe promulgated the view that this change is also effected in the organism. Buchheim found that when calomel and albumen were macerated together, the presence of a soluble salt of mercury could always be detected[1] in the filtrate obtained from them. The amount which is obtained by passing a stream of hydrogen sulphide through the solution is certainly not large, but quite sufficient to show that when calomel is mixed with the albuminous contents of the intestines, a portion may, as it passes along the alimentary canal, be rendered soluble, and then be readily absorbed by the lymphatics. The presence of sodium chloride prevents the precipitation of any albuminate of mercury, if the latter is not itself perfectly soluble. This accords with the observations of Fürbringer to which I have already referred, namely, that metallic mercury when introduced into the circulation is transformed to some extent into a soluble compound.

In this way, then, calomel becomes absorbed into the system, and produces its effects there in harmony with the facts which have been formerly established by clinical observation.

The syphilitic poison is acted upon precisely in the same way as if the soluble perchloride had been administered, for the calomel, being transformed into a soluble compound, acts upon it through the medium of the circulation. The typhoid poison in the small intestines, in the early stages of the disease, is brought into direct contact with the resulting soluble compound of mercury, and must have its action considerably attenuated thereby, as these soluble mercurial compounds have a very distinct poisonous effect on all micro-organisms; the temperature is lowered, and the course of the disease is rendered shorter and milder.[2]

[1] G. v. Oettingen, 'Dorpater Dissertation,' 1848. In Buchheim's 'Beiträgen,' 1849, S. 33; Voit, loc. cit., S. 85.

[2] Lesser, 'Die Entzündung und Verschwärung der Schleimhaut des Verdauungs canals,' u. s. w., Berlin, 1830, with plates; Wunderlich, 'Arch. f. physiolog. Heilkunde,' 1857, S. 367; Liebermeister, 'Arch. f. klin. Med.,' 1868, Bd. iv, S. 421; L. Traube, 'Gesammelte Beiträge,' 1871, Bd. ii, S. 270.

This does not result from the laxative action of the remedy, for no beneficial effect follows the administration of other purgatives—in fact, they generally do harm by increasing the intestinal ulceration. The summer diarrhœa of children is frequently relieved by small doses of calomel, such as 0·01 to 0·1 gramme ($\frac{1}{6}$ to $1\frac{1}{2}$ grains). The diarrhœa probably arises from the presence in the intestine of some foreign ferments, which develop there and cause irritation and decomposition. The administration of an antiseptic remedy destroys the ferment, and the cause being removed the disorder subsides. If the perchloride is administered it will probably be absorbed in the upper part of the intestines, and consequently not come in contact with the ferment. The state of affairs is very much the same, it appears to me, as when we endeavour to lessen or remove the exciting cause of dysentery by carefully administering enemata containing the perchloride of mercury. It is immaterial whether the remedy is administered by the mouth or by the rectum, so long as it comes in contact with the morbific agent. The violent diarrhœa which follows the exhibition of large doses—0·2 to 1·0 gramme (3 to 15 grains)—of calomel is due to the direct irritation of the soluble mercurial compound which has been formed.

The term calomel stools has been applied to the copious dark green evacuations which result from large doses of the drug. They contain unaltered calomel, black mercuric sulphide, and undecomposed bile.

The presence of the last was proved by Fr. Simon.[1] He observed that the calomel stools were liquid, of a dark green colour, without any fæcal odour, and exhaled on evaporation an odour similar to that from saliva or organic extracts when similarly treated: the bile salts and the biliary colouring matter were present in large quantities. Other investigators[2] have confirmed this, and made further experiments on the subject. Three specimens, each of 100 c.c., of ox bile were used; to one three grammes of calomel were added, to another two grammes, and none to the third. All three

[1] Fr. Simon, 'Handb. der angewandten med. Chemie,' 1841, Bd. ii, S. 496.

[2] Wassilieff, 'Zeitschr. f. physiol. Chemie,' 1882, Bd. vi, S. 112.

were placed in a warm room and shaken up from time to time. The two specimens to which calomel had been added immediately assumed a grass-green colour, and retained this colour during the six days the experiments lasted; they reacted in the usual way to Gmelin's test for bile pigment, and showed no trace of decomposition. The third specimen, to which no calomel had been added, within twenty-four hours became brownish yellow, no longer reacted to the test for bile pigment, and rapidly underwent decomposition.

Evidently some of the calomel was acted upon by the organic substances contained in the bile, and being dissolved, pervaded the fluid and prevented its decomposition. The same effects are produced in the intestines. Under normal conditions the bile pigments—bilirubin and biliverdin—are converted, as the result of putrefactive changes, into hydrobilirubin, and consequently the former cannot be detected in the fæces. Calomel checks the putrefactive changes in the intestines, for Fr. Simon had already noticed the absence of odour in the calomel stools; the bile pigments consequently remain to a great extent unchanged, and as a result of the increased peristalsis quickly appear in the evacuations. Indol, a putrefactive product, and one of the substances to which the offensive odour of fæces is due, is absent according to Wassilieff in the calomel stools of dogs; but leucine and tyrosine, two pancreatic products which, under normal conditions, are decomposed in the intestine, are always present.[1] In connection with this it is of interest to note that the presence of calomel does not prevent the digestion of albuminous material by the gastric juice, nor the disintegration of fat by the pancreatic secretion. It appears, therefore, that calomel acts only on organised ferments,—that is, upon the cells only, not upon their products.

These statements, and the explanation above given, are, on the other hand, strongly controverted.[2] Both sides are so positive in their assertions, that it seems to me not improbable that essentially different effects may result from

[1] J. Radziejewsky, 'Arch. f. Anat. u. Physiol.,' 1870, S. 55.

[2] Fr. Müller, in C. Gerhardt's 'Mitteil. a. d. med. Klinik zu Würzburg,' 1886, ii, S. 365.

variations in the contents of the intestines, dependent upon the kind of food and the state of its digestion.

Intimately connected with what has been described with regard to the action of calomel on the bile, is the answer to a question which has been much discussed, especially in England, namely, whether or not calomel increases the secretion of bile. It has long been supposed that it does increase the secretion, owing to the copious biliary evacuations which follow its use. We can now give a satisfactory explanation as to the production of these biliary evacuations.

There may be, however, at the same time an increased secretion of bile, and numerous investigations have been undertaken on this point. Kölliker and H. Müller found that the administration of calomel to a dog with a biliary fistula lessened[1] the total amount of bile secreted. According to H. Nasse[2] there is a diminution of the fixed constituents of the bile, but an increase in the absolute amount of water. Rutherford[3] arrived at the following conclusion :—Calomel, when introduced into the duodenum of a fasting dog in repeated doses of 0·12 to 0·6 gramme (1·8 to 9 grains), produces diarrhœa in proportion to the dose. But so far from increasing the secretion of bile, it distinctly diminishes it. The perchloride, however, when introduced into the duodenum, even in doses of 0·003 gramme ($\frac{1}{22}$ of a grain), considerably increases the secretion. The results varied consequently according to the circumstances. In the one case we have the soluble perchloride acting upon the upper part of the alimentary canal; in the other we have a somewhat similar compound gradually formed in the lower part of the intestines.

The use of calomel as a DIURETIC in heart disease, for which purpose it was employed in former times, has recently been revived.[4] It is administered in doses of about 0·2

1 Kölliker und H. Müller, 'Würzburger Verhandlungen,' 1855, Bd. v, S. 231.

2 H. Nasse, "De bilis copia et indole,' ref. 'Jahresber. d. Med.,' 1858, i, S. 155.

3 Rutherford, 'Transact. Roy. Soc. Edinburgh,' 1879, Bd. xxv, S. 237.

4 E. Jendrassik, "Das Calomel als Diureticum," 'Arch. f. klin. Med.,' 1886, Bd. xxxviii, S. 499; 1891, Bd. xlvii, S. 226; R. Stintzing, bid., 1888, Bd. xliii, S. 206.

gramme (3 grains) three times a day for some days, and if stomatitis or diarrhœa is not induced (to obviate which, washes for the mouth containing potassium chlorate are used, and opium is given internally) the increase in the flow of urine is much greater than results from the action of any other known remedy. It is ineffectual in pleural exudations and in dropsy associated with renal disease, cirrhosis of the liver, or general decline. The action depends upon direct stimulation of the secreting epithelium of the kidneys. Calomel acts in the same way on healthy individuals, but to a much less extent than in cases of heart disease.

Calomel, after being highly pulverised, is also applied locally in syphilitic and other affections of the eye. Oculists formerly supposed that, being insoluble, its action was purely mechanical. Kammerer,[1] however, demonstrated that when applied in this way it was actually absorbed into the system. After sprinkling calomel inside the eyelids he detected the presence of mercury in the urine, which could only result from the calomel being transformed into some soluble compound, either in the conjunctival tissue or in the lachrymal secretions.

When applied in this way it is very important to bear in mind that potassium iodide must not be simultaneously administered, for if it is, violent inflammation of the eye will be produced, a fact which Fricke demonstrated more than fifty years ago. The same result has since been frequently observed, and has also been confirmed by experiments on animals.[2] The reason is clear. When potassium iodide is taken internally, it appears within a few minutes in the lachrymal secretions, where its presence can be detected so long as the salt remains in the circulation. Potassium iodide was administered internally to some rabbits, and subsequently calomel was sprinkled on their conjunctivæ. The powder immediately turned a greenish-yellow colour, and the eye became inflamed. Moreover inflammation of the eye of a rabbit was quickly induced, by painting the conjunctiva with the greenish-yellow precipitate obtained by mixing together

[1] Kammerer, 'Arch. f. pathol. Anat.,' 1874, Bd. lix, S. 459.

[2] W. Schlaefke, 'Arch. f. Ophthalmologie,' 1879, Bd. xxv, S. 251; F. Baumeister, 'Berl. klin. Wochenschr.,' 1884, S. 688.

potassium iodide and calomel. This precipitate of Hg_2I_2, mercurous iodide, is readily dissolved and easily decomposed in the lachrymal secretion when the latter contains sodium chloride and potassium iodide, and consequently sets up irritation there much more rapidly than calomel, which is less soluble and less easily acted upon.

This greenish-yellow colour is also produced when potassium iodide is administered internally and calomel applied locally to an individual suffering with flat condylomata. The growths become coated with mercurous iodide and shrivel. It may be remarked in passing that these growths are also destroyed if simply sprinkled over repeatedly with calomel; and this is effected still more rapidly if, previous to each application, the growths are painted over with a solution of sodium chloride. The reason for this is quite intelligible from what has been already stated. The soluble mercurial salt penetrates into the morbid cells and paralyses them. Other antiseptic powders, such as salicylic acid, iodoform, naphthalin, &c., produce the same effect, but none of them act so energetically as calomel.[1]

If any proof were necessary in support of the view that syphilis is ameliorated or cured by mercurial preparations, and that the latter attack and destroy both the syphilitic poison and the morbid growths resulting from it, this proof is to be found in the direct, slow and painless action which calomel exerts on these superficial condylomata. That any "tonic" effect is produced in the affected cells is quite out of the question, for they are themselves liquefied under the action of the remedy. The same effects are produced by the use of the Emplastrum Hydrargyri already referred to, and by other external applications.[2] Moreover no one could possibly assert that the tissue cells of an individual who was suffering from salivation and stomatitis under the influence of mercury were in a state of increased "tone;" nevertheless it is precisely under these conditions that syphilitic affections rapidly decline.

It is very important that, in whatever way it is employed,

[1] P. Fürbringer, "Zur localen Wirkung des Calomels bei Syphilis," 'Zeitschr. f. klin. Med.,' 1884, Bd. viii, S. 594.

[2] H. Köbner, 'Deutsch. med. Wochenschr.,' 1884, S. 757.

the non-poisonous calomel should be absolutely FREE from any trace of the poisonous PERCHLORIDE. The presence of the latter may be determined by the following simple test:—Take a clean knife, put on it a drop of water, and then add to it a few grains of the suspected calomel. On washing the blade after the lapse of a minute no dark stain should be visible. I here show you the experiment both with a pure specimen of calomel and with one contaminated with the perchloride. In the latter case you see the black spot of magnetic oxide which has been produced by the immediate separation of a little chlorine from the sublimate.

It is also of importance, when ordering calomel in the form of pill or powder, to remember that organic substances, such as cane-sugar, may convert it partially into the sublimate, especially if the mixture gets damp. Such preparations, therefore, should not be kept any length of time.[1] In the presence of organic substances and exposed to the light, calomel may be converted into mercurous oxide, Hg_2O, which is black, and gives the mixture a grey or black colour, according to the quantity present.

With these two compounds of mercury and chlorine the two compounds of iodine run chemically parallel. They are the HYDRARGYRUM BINIODATUM, Hydrargyri Iodidum Rubrum, mercuric iodide, HgI_2; and the HYDRARGYRUM IODATUM, Hydrargyrum Iodidum Viride, mercurous iodide, Hg_2I_2 or HgI. The first is a powder of a vermilion colour, which when heated in a glass tube becomes yellow, melts, and is volatilised; it dissolves sparingly in alcohol, and is almost insoluble in water, differing in this respect essentially from the perchloride. It is prepared by mixing together a solution of mercuric perchloride with a solution of potassium iodide, when the mercuric iodide is precipitated, $2KI + HgCl_2 = 2KCl + HgI_2$. This is readily soluble in an excess of potassium iodide. Mercurous iodide is a greenish-yellow amorphous powder, insoluble in alcohol, very sparingly soluble in water, and is volatilised by heat. It is prepared by rubbing together eight parts of metallic mercury with five parts of iodine. When exposed to the light, the surface gradually becomes black; if exposed to direct sun-

[1] E. Schmidt, 'Lehr. d. pharmaceut. Chemie,' 1887, Bd. i, S. 905.

shine, the change takes place almost instantaneously, and is due to the liberation of mercury in a state of minute subdivision. On shaking the powder the black colour is again changed into a greenish yellow. The preparation is no longer officinal.

Both of these compounds with iodine were formerly much more used in the treatment of syphilis, than at the present time, the combination of mercury and iodine being regarded as specially efficacious.

HYDRARGYRUM CYANATUM, mercuric cyanide, $HgCy_2$, has been made officinal in the German Pharmacopœia in order to furnish practitioners with a preparation for subcutaneous use, in the treatment of syphilis, which is readily soluble, and which causes no irritation. It consists of colourless, transparent, dimetric prisms, which are soluble in thirteen parts of water, and are volatilised by heat without leaving any residue. The solution has a neutral reaction, and does not precipitate albumen. The distillation of mercuric cyanide with a dilute acid affords a convenient way, chemically, of obtaining hydrocyanic acid. The latter is probably also formed slowly in the body when the salt is injected, but the amount derived from the dose employed, 0·003 to 0·005 gramme ($\frac{1}{20}$ to $\frac{1}{14}$ of a grain), is so small that its effect need not be taken into account. A 1 per cent. solution of this preparation was injected 1650 times, and only on ten occasions did the injections give rise to the formation of an abscess, which occurred four times in the same individual.[1] According to the observations made upon the syphilitic cases in the hospital at Bonn, the administration of the remedy was painless in two thirds of the patients, and in one third was followed by pain of two hours' duration.[2]

Its internal administration has been recommended in cases of diphtheria,[3] given in hourly doses of 0·0003 to 0·001 ($\frac{1}{200}$ to $\frac{1}{70}$ of a grain) in water.

[1] P. Prochorow, 'St. Petersb. med. Wochenschr.,' 1885, S. 88.

[2] J. Schütz, 'Deutsch. med. Wochenschr.,' 1885, S. 215; J. Nega, 'Vergleichende Untersuchungen über die Resorption und Wirkung verschiedener zur cutanen Behandlung verw. Quecksilberpräparate,' Strassburg,' 1884.

[3] Hugo Schulz, 'Deutsch. med. Wochenschr.,' 1884, No. 1.

Perchloride of mercury decomposes even in distilled water, calomel being precipitated. If organic substances are present, the change takes place more rapidly.[1] The taste and appearance of mixtures containing organic substances are consequently changed, the organic substances, as Berthelot pointed out, being oxidised by the perchloride. The same may be said of the solution, now very generally employed, which is a mixture of a solution of the perchloride (1 in 1000 to 5000) with one of sodium chloride (0·5 in 100). This when kept and exposed to the light deposits a precipitate of calomel, oxygen is liberated, and the solution contains free hydrochloric acid. Half of the chlorine from the perchloride acts upon the water and decomposes it:

$$2HgCl_2 + H_2O = 2HgCl + 2HCl + O.$$

Ordinary spring water is, therefore, not a good vehicle with which to prepare solutions of the perchloride. The bicarbonates of the alkaline earths quickly decompose it, forming the trioxychloride and the tetraoxychloride (Hg_4O_3Cl and $Hg_5O_4Cl_2$), which being insoluble are precipitated, whilst the supernatant liquid contains little or none of the perchloride.[2] The addition, however, of some free acid—such, for instance, as ordinary vinegar (1 part to 125) or tartaric acid—will prevent this decomposition.

Solutions of the perchloride, however dilute they may be, must not be prepared in metallic vessels, as the metal attracts the chlorine and decomposes the perchloride.

[1] Berthelot, "Observations sur la décomposition du tartre émétique et du sublimé corrosif par quelques substances végétales," in Fourcroy's 'La médecine éclairée,' &c., 1791, vol. i, p. 261.

[2] Fürbringer, "Ueber illusorische und pracktisch verwertbare Sublimatlösungen in Brunnenwasser," 'Deutsch. Med.-Zeit.,' 1886, No. 63.

The preparations of mercury, when administered in a reasonable and intelligent way, may be classed among our most reliable and useful remedies. Severe cases of syphilis are generally cured by their use; but, like all other active drugs, they produce poisonous effects when given under unsuitable conditions or in improper doses.

For this reason there is appended to each mercurial preparation in the German Pharmacopœia (as in the case of all other poisonous remedies) a carefully adjusted "maximum dose." The largest dose which the apothecary is allowed to dispense of the cyanide, perchloride, iodide, and of the two oxides is 0·02 gramme ($\frac{3}{10}$ of a grain), unless the physician indicates on the prescription that a larger dose has been advisedly ordered, by attaching to the dose the special mark (!). For the subchloride (calomel) no maximum dose is indicated, as it is administered as a purgative in doses as large as 1 gramme (15 grains), and when given to this extent it passes so rapidly through the intestinal canal that very little can possibly be absorbed. The Swiss Pharmacopœia fixes the maximum dose at 0·5 gramme (7½ grains), of which I entirely approve; for by limiting the dose in this way we lessen the possibility of excessive and injurious irritation being set up in the alimentary canal, owing to the large amount which, inadvertently, the physician may have prescribed.

Metallic mercury vaporises even at the ordinary temperature, and may produce poisonous effects if the evaporating surface is considerable, or if the emanations from it continue for any length of time. I will give you three instances of the kind; one occurred some years ago, the others more recently.

"The 'Triumph,'[1] of seventy-four guns, arrived in the harbour of Cadiz in the month of February, 1810; and in the following March a Spanish vessel, laden with quicksilver for the mines of South America, having been driven on shore by a gale of wind and wrecked under the batteries, then in the

[1] Dr. Burnett's account of the effect of mercurial vapours on the crew of His Majesty's ship "Triumph" in the year 1810, 'Philos. Transactions,' 1823, Part 2, p. 402. Communicated by Matthew Baillie, M.D., F.R.S.

possession of the French, the boats of this ship were sent to her assistance, by which means, during many successive nights, about one hundred and thirty tons of quicksilver were saved and carried on board the 'Triumph,' where the boxes containing it were principally stowed in the bread-room.

"The mercury, it appears, was first confined in bladders, the bladders in small barrels, and the barrels in boxes. The heat of the weather was at this time considerable, and the bladders having been wetted in the removal from the wreck, soon rotted, and the mercury, to the amount of several tons, was speedily diffused through the ship, mixing with the bread, and more or less with the other provisions. The effect of the accident was soon seen by a great number of the ship's crew, as well as by several of the officers being severely affected with ptyalism, the surgeon and purser being amongst the first and most severely affected by the mercury flowing constantly into their cabins from the bread-room, their cabins being, as is usual on the orlop deck, separated from the store by partitions of wood. In the space of three weeks from the mercury being received on board, two hundred men were afflicted with ptyalism, ulcerations of the mouth, partial paralysis in many instances, and bowel complaints. These men were removed into transports, where those more slightly affected soon got well; but fresh cases occurring daily, Rear-Admiral Pickmore, then in command of the squadron, ordered an inspection to be made by the surgeons thereof, and in consequence of their report sent the 'Triumph' to Gibraltar to remove the provisions, and purify the ship by ablution, the affected men being sent to the Naval Hospital; which order was strictly attended to, the provisions, stores, and likewise the shingle ballast being removed on shore.

"Notwithstanding the removal of the provisions, &c., and afterwards frequent ablution, on re-stowing the hold, every man so employed, as well as those in the steward's room, was attacked with ptyalism; and during the ship's passage, and on her return to Cadiz, the fresh attacks were daily and numerous till the 13th of June, when the 'Triumph' sailed for England.

"On their departure from Cadiz they experienced fresh breezes from the north-east, and the men being kept constantly on deck, the ship aired night and day by windsails, the lower deck ports allowed to be kept open at all times when it could be done with safety, allowing no one to sleep on the orlop deck, and none affected with ptyalism on the lower deck, a very sensible decrease in the number daily attacked soon became apparent; but nevertheless many of those already affected became worse, and they were under the necessity of removing twenty seamen and the same number of marines, with two sergeants and two corporals, to a sloop of war and the transports in company. On their arrival in Cawsand Bay, near Plymouth, on the 5th of July, not one remained on the list for ptyalism.

"The effects of the mercurial atmosphere were not confined to the officers and the ship's company: almost all the stock, consisting of sheep, pigs, goats, and poultry, died from it; mice, cats, a dog, and even a canary bird shared the same fate, though the food of the latter was kept in a bottle closely corked up.

"The Surgeon (Mr. Plowman) informed me in conversation that he had seen mice come into the ward-room, leap up to some height, and fall dead on the deck.

"The 'Triumph,' previous to this event, had suffered considerably by having a number of her men attacked with malignant ulcer, which at one time prevailed to a considerable extent in our ships both at home and abroad; and in many of the men who had so suffered, the ulcers, which had long been completely healed without even an erasure of the skin, broke out again, and soon put on a gangrenous appearance.

"The vapour was very deleterious to those having any tendency to pulmonic affections; three men died of phthisis pulmonalis, who had never complained or been in the list before they were saturated with the mercury; and one man who had suffered from pneumonia, but was perfectly cured, and another who had not had any pulmonic complaint before, were left behind at Gibraltar, labouring under confirmed phthisis. Two only out of so large a number affected died from ptyalism, gangrene having taken place in their cheeks

and tongue: they had previously lost all their teeth. In the case of a woman, who was confined to bed in the cock-pit with a fractured limb, not only were all the teeth lost, but many exfoliations also took place from the upper and lower jaws.

* * * * *

"In a communication with which Mr. Plowman, Surgeon of the 'Triumph,' has obliged me, he states that those who messed and slept on the orlop and lower decks, with the exception of the midshipmen, suffered equally, while those on the main or upper deck were not so severely affected: the men who lived and slept under the forecastle escaped with a slight affection of the gums. The only reasons which can be assigned for the partial escape of the midshipmen are that the windsails were kept always in action, and that these gentlemen were almost constantly on deck, or were more frequently employed on service out of the ship, in proportion to their numbers, than the men."

The two following cases are of recent date.

A lady, twenty-five years of age, suffered from periostitis of the alveolar processes of the lower incisors, accompanied by severe pain; the teeth themselves were sound. On applying ice the pain gradually ceased. After a time the pain in the jaw returned. On examining the part it was found to be extremely sensitive to the touch, the submaxillary glands on both sides were swollen, there was extensive stomatitis with commencing ulceration of the gums, salivation, and an offensive odour about the mouth. Notwithstanding the constant use of potassium chlorate as a wash, at the end of a week no change was observable in the symptoms. The urine was then tested for mercury, and its presence was detected therein, although none had been taken by the patient. On examining the bedroom, it was discovered that some of the mercury with which the backs of two new mirrors were heavily coated had vaporised. The metal was found in the outer frame in numberless small globules, and the silvering of the mirrors had been done so badly that it was detached by the least touch of the finger. Mercury was also found in the husband's urine, though he slept further away from the mirrors. He had complained

of headache on waking in the morning. After the removal of the mirrors the unpleasant symptoms in both patients quickly disappeared, neither could mercury any longer be detected in the urine.[1]

The other, which is an instructive case, ran a much less satisfactory course, both as regards the patient and the credit of the physicians.

An unmarried lady, thirty years of age, suffered for four years from extremely severe suppuration of the gums, an unpleasant odour in the mouth, swelling of the sublingual and submaxillary glands and of the tongue, accompanied by severe darting pains of the lower jaw, which spread further after sleeping, and were intensified by speaking or eating. She became anæmic, and suffered from extreme mental irritability. The symptoms all improved in the summer when she was away from home. Numerous physicians and specialists were consulted. Scurvy from poverty of blood, reflex irritation arising from the condition of the pelvic organs, carious teeth, neuralgia due to trophic disturbances, &c., were diagnosed, and the patient treated in accordance therewith—in each case, unfortunately, without the slightest benefit. During the whole four years no one had ever suspected chronic poisoning. Dr. Neukirch, however, tested the urine of this unfortunate individual for mercury, and found a very distinct amount. Its presence was due to the faulty coating or silvering of a large mirror which adorned the romantic oriel window of this lady's house in Nuremberg. Here in the cold weather she had sat from day to day with closed windows, breathing the metallic vapours for years. When the cause was removed the effects quickly passed off, leaving little trace behind.

Tremor of the limbs is not infrequently an early and prominent symptom of mercurial poisoning. It generally begins in the hands, and then the muscles of the body and the face are affected. Headache and giddiness are also associated with it. The tremor only ceases when the patient lies down quietly or sleeps. It is augmented by mental emotion, and may be accompanied by spasmodic contractions and by painful tonic flexions and extensions of

[1] R. Neukirch, 'Berlin. klin. Wochenschr.,' 1883, S. 820.

the muscles. The electric excitability is unchanged, the cutaneous and tendinous reflexes are increased. There is generally increased mental irritability; a casual remark may suffice to discompose the patient, to flush his face and excite him. The memory and judgment may, however, remain unaffected.[1]

The above is a brief description of the more important of the many variable symptoms which in general characterise mercurial poisoning. As we are aware, the vapour of metallic mercury is rendered soluble by the mucous membranes, and is consequently there converted into the same compound as is the case with all other mercurial preparations which pass into the circulation. Numerous experiments[2] on warm-blooded animals have produced similar results.

If a large quantity of any soluble compound of mercury is introduced into the circulation, the first symptom which shows itself is IRRITATION OF THE INTESTINES. There are copious, often bloody evacuations, which are accompanied by pain and tenesmus. Vomiting sometimes takes place, and generally there is salivation. The respirations become frequent, irregular, and intermittent, the action of the heart is enfeebled, and sudden paralysis of the organ sometimes occurs. There is general tremor and psychical disturbance of the animal, and death takes place preceded by convulsions due to asphyxia. The irritability of the muscles is not sensibly altered, neither is the condition of the blood. Death results from paralysis of the heart and of the respiratory centre.

If the dose of the mercurial compound is carefully adjusted, the animal, for the first few days, appears to be unaffected by it, but dies some time afterwards. I now

[1] Stadthagen, 'Deutsch. med. Wochenschr.,' 1884, S. 202.

[2] R. Overbeck, loc. cit., S. 108; Saikowsky, 'Archiv f. pathol. Anat.,' 1866, Bd. xxxvii, S. 347; J. Rosenbach, 'Zeitschr. f. rat. Medicin,' 1868, Bd. xxxiii, S. 36; Radziejewsky, 'Arch. f. Anat. u. Physiol.,' 1870, S. 22; Harnack, 'Arch. f. exper. Path. u. Pharm.,' 1874, Bd. iii, S. 59; M. Heilborn, 'Arch. f. exper. Path. u. Pharm.,' 1878, Bd. viii, S. 361; v. Mering, ibid., 1880, Bd. xiii, S. 86; L. K. Lazarewic, Doctor-dissert., Berlin, 1879; J. L. Prevost, 'Étude expérimentale rel. à l'intox. par le Mercure,' Genève, 1883.

inject into the jugular vein of this vigorous rabbit, which weighs 2400 grammes, 0·015 gramme of corrosive sublimate dissolved in 1 c.c. of a 1 per cent. solution of sodium chloride. It remains quite lively, and immediately begins to eat the lettuce placed before it. To-morrow its fæces will be moist, the following day thin and watery, the symptoms above described will show themselves, and on the fifth day there will be a considerable fall in its temperature, and death will take place from paralysis of the nervous centres and of the heart. Here are the intestines of an animal which was poisoned five days ago, and which present the following appearances:

Catarrh, hyperæmia, and ulceration accompanied with hæmorrhage from the mucous membrane of the stomach and intestines. In the large intestine especially, and more particularly on its prominent folds, we see large ulcers with a grey coating. These may be either of a pure necrotic, diphtheritic, or typical dysenteric character;[1] occasionally they are smooth, and appear as though cut out with a punch. They are sometimes found in the small intestines, but only when they also exist in the large intestine; they are often met with in the rectum. The KIDNEYS of this animal are evidently very much changed. Even externally the change is very marked. They are pale, and feel harder to the touch than usual. On section, streaks are observed in the cortical substance perpendicular to its surface, and running thence to the medulla. I have here a longitudinal section under the microscope, from which you see that the tubules and the loops of Henle are dark in places where they are filled with a granular deposit. This dissolves on the addition of an acid, and is found to consist of calcium phosphate and carbonate.

The presence of these bony constituents in the tubules of the kidneys led to the simultaneous examination of the bones and kidneys in these animals. Prevost, and the chemist Frutiger, found that in rabbits poisoned with corrosive sublimate, the bones after being calcined yielded less ash, and the kidneys after incineration yielded more ash than under normal conditions. This was referred to the production of

[1] Eugen Fraenkel, 'Arch. f. path. Anat.,' 1885, Bd. xcix, S. 276.

irritative changes by the sublimate in the bones, resulting in a more rapid disintegration of their mineral constituents, the latter being rapidly eliminated from the system through the kidneys.[1] Regarded anatomically, this change is characterised by CALCIFICATION OF THE RENAL EPITHELIUM, and consequent upon it, the urinary secretion naturally ceases. Preceding this the urine of the rabbit was pale, transparent, increased in quantity, and frequently contained albumen or sugar.

Other substances also, such as aloin and subnitrate of bismuth, when injected subcutaneously, give rise to a considerable deposit of calcium salts in the kidney, and the same effect is produced, in a few hours, after ligature of the renal arteries.[2] This rather supports the view that mercury acts directly upon the renal epithelium, causing irritation followed by necrosis, and that the calcification results from its rapid decay.

The general use in recent years of the sublimate, as a wash for extensive wounds after surgical and gynæcological operations, has presented us with abundant instances of its poisonous action. In the cases which ended fatally, ulceration of the intestines, or calcareous changes in the kidneys, invariably existed; in some instances both organs were affected. Evidence of inflammation in the respiratory organs[3] has also been sometimes present. In cases where the mercury was used too largely, but in quantities insufficient to cause fatal effects, it gave rise to salivation, ulcerative stomatitis, with offensive discharge from the mucous membrane of the mouth, diarrhœa—invariably sudden, extremely painful, the evacuations often containing large quantities of blood, sometimes also accompanied with spasm of the bladder[4]—anæmia, feeble action of the heart, trembling of the limbs, albuminuria, and glycosuria. The offensive stomatitis is most rapidly developed in persons who are

[1] Zuelzer and C. Bruck, in the 'Doctordissertation' of the latter, Berlin, 1887.

[2] Neuberger, 'Arch. f. exper. Path. u. Pharm.,' 1890, Bd. xxvii, S. 38.

[3] H. Quincke, 'Berl. klin. Wochenschr.,' 1890, No. 18.

[4] B. Brandis, 'Grundsätze bei Behandlung der Syphilis,' 1879, S. 19.

badly nourished, and whose mouths, owing to a want of cleanliness, or to the existence of decayed teeth, are prepared for it. In toothless individuals the stomatitis is developed much less rapidly. Severe inflammation of the mouth may occur without the salivary secretion being either modified or increased; and, on the other hand, profuse salivation may occur without any change whatever taking place in the mucous membrane of the mouth,[1] but this is rare. In all these cases no change can be detected in the condition of the blood.

It is unquestionably difficult to offer any explanation of the poisonous action of corrosive sublimate which will apply to all its various forms. It is certainly not poisonous from its caustic action, in the ordinary sense of that term, any more than arsenic and phosphorus are. Like them, the sublimate is specially attracted to certain organs on which, through the agency of the circulation, it exerts its destructive influence, until at last by paralysing the nervous centres it kills the individual. It appears to me that everywhere in the organism it meets with protoplasm which is specially sensitive to its influence—as has been already demonstrated with respect to the cells in general of the lower organisms—which it irritates and over-stimulates, with resulting necrosis and destruction.

Another explanation,[2] based upon the results of post-mortem examinations and experiments on animals, is as follows:—The poisonous action of corrosive sublimate essentially depends upon the change which it produces in the blood. Large doses cause the blood to coagulate in the heart, in the large vessels, and in the extensive capillary region. There is considerable blocking of the pulmonary capillaries, against which the heart struggles, until at last the tricuspid valve becomes incompetent; hence the distension of the venous system, and the emptiness of the arterial system. There is everywhere stasis of the inspissated blood and the formation of red thrombi. In the intestines this stasis leads to necrotic destruction of the mucous

[1] Sigmund, 'Wiener med. Wochenschr.,' 1866, S. 793 u. 809.

[2] E. Kaufmamn, 'Die Sublimatintoxication,' Breslau, 1888; also in the 'Arch. f. path. Anat.,' 1889, Bd. cxvii, S. 227.

membrane. The tops of the folds are the portions where it chiefly takes place, and there simply mechanically. In the affected spots, especially in the large intestine, numerous bacteria settle themselves, and develop the diphtheritic and dysenteric conditions of the mucous membrane. The appearances in the kidneys are attributed to necrosis of the epithelium, resulting from the arterial anæmia. The lime is deposited in the dead renal epithelium precisely in the same way as when degeneration of these cells is brought about by ligature of the renal artery.

In more recent investigations[1] objections are raised to this view of the matter; and it is further asserted that coagulation of the blood and blocking of the vessels in the manner suggested do not occur. I agree with this view. As I have already stated, the perchloride acts, first of all, as a direct poison upon the protoplasm.

Inflammatory conditions of the skin, such as erythema and eczema, are sometimes developed from mercurial inunctions; they have, however, nothing specially characteristic about them.[2] It is uncertain whether or not these are due to the ointment being rancid or otherwise bad, or to individual predisposition;[3] they may be due to either condition. Affections of the skin sometimes follow the internal administration of mercury. Such results are, however, rare, and, as is well known, are sometimes produced by a large number of other remedies, even though the latter have been given in ordinary doses.

Corrosive sublimate is also used in baths. For an adult 5 to 6 grammes (75 to 90 grains) may be put in a full length bath; for children 0·2 to 1 gramme (3 to 15 grains) may be added, the patient remaining in the bath about half an hour. The vessel must be made of wood. The unbroken skin appears not to absorb any mercury from the bath,

[1] Marchand und W. Falkenberg, 'Arch. f. pathol. Anat.,' 1891, Bd. cxxiii, S. 567.

[2] Alexander. A case of acute general eczema following the inunction of a small quantity (not larger than a bean) of Ung. Hydr. Ammon., 'Viertelj. f. Dermat.,' 1884, S. 105.

[3] A. Peters, "A case of idiosyncracy with regard to preparations of mercury," 'Cbl. f. prakt. Augenheilk.,' 1890, October number.

but it may be very different if there is any eruption or ulceration of the skin. It is, therefore, very necessary to be cautious about the baths. Caution must also be exercised in applying ointments containing the sublimate over an extensive surface of the skin. Violent burning pain and swelling may be produced, and after a few days death may take place. This was the case with two young women suffering from the itch, whom a quack tried to cure with an ointment of that kind.[1]

For centuries there have always been a certain number of agitators, both in and out of the medical profession, who have denounced the employment of mercury in the treatment of constitutional syphilis, and have attributed to the remedy all the evil results observable in that disorder. This agitation was the natural sequel to the former ill-advised and excessive use of mercury. At the present time there is not the slightest doubt that there are characteristic differences between the results of syphilitic infection and those due to mercurial poisoning, and that the former begin to improve under the judicious use of the drug. In no instance as yet has the improper use of mercury produced iritis, gummata of the bones and other internal organs, with which we are familiar, nor has it led to the skin growths or the hyperplasia of the lymphatic glands, all of which result from the specific syphilitic infection, even in individuals who have not had a single dose of mercury.[2] Moreover mercury, when properly administered in suitable doses, by no means produces such baneful effects upon the system as have often been attributed to it.

Practically it is important to remember a fact, observed long ago, that patients whilst undergoing a course of mercurial treatment are specially liable to inflammatory affections of the lungs.

The following is an account of a case of poisoning from corrosive sublimate, taken from ancient history.

[1] Anderseck und Hamburger, 'Vierteljahrs. f. ger. Med.,' 1864, Bd. xxv, S. 187.

[2] For further details see A. Kussmaul, 'Unters. über den const. Mercurialismus und sein Verhältn. z. const. Syphilis,' Würzburg, 1861, S. 433.

Charles IX received a bezoar[1] which was said to be an antidote to poisons in general. On asking his physician, A. Paræus, if this was the case, the latter replied that it could only be determined by an experiment, which might readily be tried on some criminal condemned to death. The king ordered a cook to be brought before him, who had stolen two silver dishes, and was shortly to be hanged, and invited him to submit to the experiment, under the condition that, if it was successful, his life should be spared. The criminal readily assented. Corrosive sublimate was first administered to him, and subsequently the bezoar. After suffering intense abdominal pain for seven hours, and discharging blood from the mouth, rectum, and urethra, he died, notwithstanding that Paræus poured down his throat eight ounces of oil. An eschar of the stomach was found on post-mortem examination. After this, it pleased His Majesty to throw the bezoar into the fire.

Mercury is ELIMINATED from the system in every excretion which has hitherto been investigated. During the first half of the present century the results of a series of investigations were published, many of these were of a negative character, and it was only after the methods of investigation had been improved that there was any general agreement as to the results.[2]

The saliva is naturally the secretion in which the presence of mercury would be first sought for, since the salivary glands are so quickly affected by it. FALLOPIO (obiit 1562) asserted that if a gold coin is held in the mouth of an individual who is suffering from salivation, the mercury is precipitated upon it. Upon gently heating the coin the mercury evaporates, and so by repeating the process a part of the mercury is abstracted from the mouth, and its

[1] A. Paræus, "De Venenis," 'Op. Chirurg.,' lib. xx, cap. 36:— "Bezoar stones are concretions found in the stomach and intestines of certain ruminants. In former times those found in the abomasum of the Eastern wild goats and antelopes were held in high esteem. Their chief constituents are said to be calcium phosphate, mucus, and a small amount of bile."

[2] F. C. Schneider, 'Sitzungsber. d. Wiener Akademie,' 1860, Bd. xl, S. 239.

baneful effects prevented. Lehmann[1] demonstrated the presence of mercury in the saliva in several instances.

We know, from the experiments, already referred to, of G. Lewald upon calomel, that mercury is excreted in the milk. Its presence was detected in the milk of a syphilitic woman who was being treated by mercurial inunction, and the child she was nursing, and which was also affected, got well without any other treatment.[2] That it appears in the cutaneous secretions is clearly shown by the fact, that an amalgam forms on the gold rings and other ornaments of persons who are taking mercury. After administering the perchloride, this has been detected in the perspiration, and after the iodide of mercury has been given, it is also transformed into a chloride, and as such can also be detected in the cutaneous secretion.[3]

Oberländer summarises the results of his experiments as follows :—The natural and spontaneous elimination of mercury, through the medium of the urine, when unaffected by other remedies, goes on for 190 days after its use is discontinued. During this period the amount eliminated varies from time to time, and the process may even be entirely suspended for as long as ten days.

Schuster,[4] of Aix-la-Chapelle, as the result of exhaustive investigations arrives at the following conclusions :—During the administration of mercury a considerable proportion of it very soon begins to pass off in the fæces. Its elimination appears invariably to take place in this way, and to continue to a marked degree for some weeks after the course of treatment has been stopped. At the end of a year after its discontinuance, no mercury can be found in the fæces. During the treatment the mercury may also be eliminated by the urine, but not so constantly as by the bowels. Six months after discontinuing the remedy its presence can no longer be detected in the urine. That mercury can remain as long as twelve months in the system—a statement which the anti-mercurialists specially emphasised—is consequently improbable.

[1] Lehmann, 'Lehrbuch d. physiol. Chemie,' 1853, Bd. ii, S. 22.
[2] E. Klink, 'Arch. f. Dermat. u. Syph.,' 1876, S. 207.
[3] Bergeron und Lemattre, ref. 'Cbl. f. d. med. Wiss.,' 1864, S. 656.
[4] Schuster, 'Vierteljahrs. f. Dermat. u. Syph.,' 1881, S. 51.

To demonstrate the presence of mercury in the excretion, it is first of all necessary to decompose the organic matters by heating them with potassium chlorate and hydrochloric acid. The mercury is thereby converted into a chloride. Any excess of chlorine is expelled by careful evaporation. The residue is mixed with water and filtered. The filtrate is then subjected to electrolysis, a gold cathode and platinum anode being used. The mercury is deposited on the gold cathode in the form of a fine grey coating, and can then be further tested in the usual manner. These are the essential parts of the process. The general details can be found in the ordinary works on analytical chemistry.[1] When properly carried out this test is so delicate that the presence of the sublimate can be detected in a solution whose strength is not greater than 1 in 1,000,000.

As regards the general distribution of the mercury in the system in cases of poisoning, it was found[2] that the colon contained the largest amount, except in those cases in which death took place soon after its administration, when the colon contained very little, and the greater part was found in the stomach and small intestines. The liver and kidneys generally contained a large amount, the spleen somewhat less, and the other organs contained still less or none at all.

The relatively large amount of mercury which is found in those cases of poisoning which do not terminate rapidly, explains why the ulcerative condition is more marked in the colon than elsewhere. Evidently, as is the case with other metallic compounds, mercury is excreted from the system to a great extent through the walls of the intestinal canal.

There is still another preparation of mercury to which I will briefly refer—it is only employed externally,—HYDRARGYRUM PRÆCIPITATUM ALBUM, Hydrargyrum Ammoniatum, white precipitate, or ammoniated mercury; and the ointment pre-

[1] For full directions how to carry out the investigation see v. Lehmann, "Exper. Unters. über die besten Methoden, Blei, Silber und Quecksilber bei Vergiftungen im tier. Organismus nachzuweisen," 'Zeitschr. f. physiol. Chemie,' 1882, Bd. vi, S. 1.

[2] E. Ludwig u. Zillner, 'Wien. klin. Wochenschr.,' 1889, No. 45, und 1890, Nos. 28 bis 32.

pared from it, the UNGUENTUM HYDRARGYRI ALBUM seu AMMONIATUM. The former is an amorphous powder, insoluble in water and alcohol, soluble in hydrochloric acid, and entirely volatilised, without fusing, at a temperature under redness, being thereby decomposed into calomel, nitrogen, and ammonia. It is prepared by dissolving two parts of corrosive sublimate in forty parts of water, and adding to the solution three parts of ammonia. The following formula represents the changes which take place—

$$HgCl_2 + 2NH_3 = NH_4Cl + HgCl.NH_2,$$

amido-chloride of mercury, or mercury-ammonium chloride being formed,—that is, corrosive sublimate in which one atom of chlorine is replaced by NH_2. Mixed with nine parts of vaseline it forms the above-mentioned ointment, which is used almost as a specific, in cases of erythematous and eczematous eruptions of the skin. We do not know whether it is absorbed or not, when applied to limited portions of the cutaneous surface. It is quite possible that some of it is absorbed, but if so, most certainly without causing, as a rule, any bad effects. Neither can we explain why the white precipitate acts so rapidly and beneficially in many simple cutaneous eruptions. The preparation has no caustic action.

We must include here a certain group of vegetable remedies, which both historically and therapeutically have been associated with mercury, and which have been constantly used in the cure of syphilis from the commencement of the sixteenth century down to the present day. The simple treatment of this disease by moderate doses of mercury has now, however, pushed these remedies into the background. They are guaiacum wood, and the roots of sarsaparilla, sassafras, and rest-harrow.

LIGNUM GUAIACI, guaiacum wood. The heart-wood, reduced to the form of chips, raspings, or shavings, of the

Guaiacum officinale, an evergreen tree growing in the West Indian islands, and belonging to the Nat. Ord. Zygophyllaceæ. It has an aromatic odour when heated, the taste is somewhat acrid. The essential ingredient of the heart-wood is the resin, of which it contains a large quantity.

The resin is either a natural exudation, or is obtained by heating logs of wood, and collecting the melted resin as it runs from them, or it is extracted by means of alcohol. When quite fresh it has a yellow or reddish-brown colour, and is transparent; but the surface is soon covered with a green powder, and the resin is then opaque. It is a mixture of resinous acid, colouring matter, a little gum, and a few mineral constituents.[1] Its alcoholic solutions assume a blue colour in the presence of oxidising agents. I pour a few drops of this yellowish-red tincture on a white plate, and hold it over the mouth of a bottle containing fuming nitric acid. The tincture immediately assume a deep blue colour. If I add a few drops of chlorine water to the tincture, the same colour is at once developed. The same colour is produced if, after rubbing down portions of plants containing protoplasm, and mixing them with water, I add a few drops of the tincture to the watery extract. The colour produced with the fuming nitric acid results from the presence of the oxidising nitrous acid, NO_2; that with the chlorine from indirect oxidation (according to the formula $2Cl + H_2O = 2HCl + O$); that with the solution of protoplasm, from the oxidation of the liberated protoplasm on its exposure to the air, whereby peroxide of hydrogen H_2O_2, or some similar compound, which readily yields nascent oxygen, is formed in the solution. Formerly this blue coloration of guaiac resin was termed the ozone reaction, since a single atom of the molecule O_3 develops it. But the reaction does not take place with the molecule O_3, but with each single atom of oxygen, from whatever source it may be obtained. A better term, therefore, is the reaction of active, nascent, or atomistic oxygen.

The addition of albumen, as I here show you, immediately discharges the blue colour.

When syphilis had rapidly extended over the whole of

[1] Hadelich, 'Journ. f. prakt. Chemie,' 1862, Bd. lxxxvii, S. 321.

Europe, diligent search was made, in every direction, for some remedy against the new plague, and it happened that one was discovered in actual use, in the country from which the infective virus had first been imported. Previous to 1508 Gonsalvo Hernandez y Quiedo,[1] who himself had suffered from the disease, brought the guaiacum wood with him from St. Domingo to Spain, and soon afterwards it was employed as an antisyphilitic all over Europe, and rapidly rose in esteem as a remedy. It was called the French wood, and none of the numerous works of the time, on venereal diseases, omitted to refer to it.

I will call your attention to one only of these works, a monograph by Ulrich von Hutten.[2] The author had himself contracted syphilis, and his physicians had grievously maltreated him with mercury. "Quas torturas, quæ supplicia sub chirurgis exhauserim? quas cruces tulerim? quantum mihi virium ex medicorum inscitia deperierit, cum tuo hæc gemitu testatus jam sæpe et apud multos sis," he exclaims in his preface.[3] . . . . "Cum ita essem aspectu et odore fœdus, et omnibus essem gravis, quibusdam odio etiam."

Dr. Stromer recommended him to try starvation diet and a course of guaiacum. The ulcerated surfaces were dressed with an ointment of white-lead, or with the froth skimmed from a decoction of guaiacum; the decoction itself was

[1] See two papers on the subject in the collected works of A. Luisinus, 'Aphrodisiacus,' &c., Leyden, 1729, S. 355.

[2] U. v. Hutten, "De Guajaci medicina el morbo Gallico,' liber unus, Mainz, 1519, 74 pages, small 4to. The work is dedicated to the Elector and Cardinal Albrecht, of Mayence. At the conclusion he states, in the shameless way which was characteristic of the period, "Quæ ita Celsitudini tuæ conscripsi, ut non vellem his quidem uti te, faxit hoc enim Servator, ne unquam debeas, sed ut in tua hæc aula essent, omnium necessitati exposita, quorum judicium a Stromero exiges tu quod præfatus sum." Heinrich Stromer was the cardinal's physician in ordinary, and was held in great esteem by Hutten; "eminet supra vulgarum medicorum sortem" is the phrase applied to him in the preface.

[3] And again, cap. vii:—"Quod tum te non ignorare scio, missos facio circumforaneos perunctores, latrones medicos, atque illos etiam indoctos doctores, ad Guajacum redeo."

swallowed, and in forty days from the commencement of this treatment Hutten was able to leave the house. Forty days later the ulcers had all cicatrised, "et depulsa omni invaletudine vires ita recepi, ut de novo factus ac renatus homo videar." This condition, however, as is well known, was not of long duration.

Not many years later—to take another classical example—about the year 1532, Benvenuto Cellini described with similar *naïveté*, his own individual experience[1] of the beneficial effects of guaiacum. He had also contracted syphilis, and was able to define the precise occasion, and now suffered from syphilitic iritis and a cutaneous eruption.

"For more than four months the disease had lain dormant, and then suddenly appeared in a most virulent form; the symptoms were not of the usual character, for I was covered over with red patches as large as a pfennig [farthing]. The doctors would not have recognised the disease had I not at once informed them of the cause, and told them my suspicions. For some time I allowed myself to be treated according to their directions, but I got no better; and at last I determined to take the wood, though it was in opposition to the wishes of the doctors, who were considered among the most eminent of those living at Rome. After I had carefully taken the remedy for some time, and been strictly dieted, I was greatly relieved, and in the course of fifty days was completely cured, and felt as lively as a fish." Cellini now exposed himself while hunting to wind and rain, and had a relapse. "I now placed myself again in the hands of the doctors, and, once more, was made much worse by their treatment. I was attacked with fever, and I determined again to try the wood. The doctors were opposed to my doing so, and declared that if I took it whilst suffering from the fever, in eight days I should be dead. I took it nevertheless, with the same care and under the same conditions as before. After drinking this holy water for four days I was altogether free from the fever, ... and in forty days I was rid of my trouble and absolutely cured."

Very few scientific investigations have been made upon

[1] See his autobiography, translated by Goethe, part 1, chap. xi.

the action of guaiacum resin. Behr[1] took doses of 4 grammes (60 grains), which produced looseness of the bowels without any colic. V. Schroff[2] states that vomiting, diarrhœa, colic, headache, deep sleep, and sometimes salivation are produced by large doses. Various accounts have been given of the diuretic, diaphoretic, expectorant, antirheumatic, and other properties which guaiac resin is supposed to possess.

RADIX SARSAPARILLÆ, sarsaparilla root, is the next substance belonging to this group. It is obtained from different species of *Smilax*, the roots of which are six feet or more in length, and about as thick as a goose-quill. The plant is indigenous to Central America, and is imported under the name of Honduras sarsaparilla. The root has a mucilaginous taste, and when chewed is faintly acrid. In addition to a large amount of starch it contains a small amount of a crystalline substance which has been termed *paralline*[3] or *smilacine*. It is soluble in twenty parts of boiling water, but almost insoluble in cold water. It belongs chemically to the glucosides. Senegine or saponine, to which I shall refer in a future lecture, is also said to be contained in this root. The action of paralline has not been investigated. Experiments with the commercial "sarsaparilline" have furnished no results worth recording.

Sarsaparilla was introduced into Europe about the year 1530, and since that time has been employed as an antisyphilitic, diuretic, and diaphoretic remedy. During the first half of last century a remedy called ZITTMANN'S DECOCTION was brought prominently into notice. This preparation, of which sarsaparilla is the chief constituent, is still used at the present day, and, indeed, with "brilliant" results, in chronic cases of syphilis as well as in other forms of that disease, when no improvement takes place under mercury and iodine, or when for other reasons it may not be advisable to administer these drugs. This is the opinion of one of our most experienced syphilologists as to the

[1] Behr, 'Meletemata de effectu nonnullarum resinarum in tractum intestinalem,' Doctordissertation, Dorpat, 1857.

[2] v. Schroff, 'Lehrbuch,' 1869, S. 380.

[3] Flückiger, 'Archiv d. Pharm.,' 1877, Bd. ccx, S. 532.

value of a remedy which has not infrequently been cast aside as worthless.[1]

The rhizome of SMILAX CHINÆ, China root, a native of China, Formosa, and Japan, is only historically of medical interest, being mentioned in a work [2] of Andreas Vesalius.

LIGNUM SASSAFRAS, sassafras, is the dried root of *Sassafras officinale*, and has a strong aromatic and sweetish taste. It is a plant of North America, belonging to the Nat. Ord. Lauraceæ, and has been used as an antisyphilitic, &c., since the year 1560. It contains about 2 per cent. of ethereal oil, consisting of *safrene* $C_{10}H_{16}$, and a liquid camphor, *safrol*, $C_{12}H_{16}O_2$.

RADIX ONONIS, rest-harrow root, obtained from *Ononis spinosa*, a plant which belongs to the Nat. Ord. Papilionaceæ, and grows wild in Germany and in Britain. The root has a somewhat sharp and sweet taste, and an odour resembling that of liquorice root. It contains certain glucosides, the medicinal action of which has not yet been investigated.

SPECIES LIGNORUM consists of five parts of guaiacum wood, three parts of rest-harrow root, one part of sassafras root, and, to improve the flavour, one part of liquorice root, all reduced to chips or shavings. From this an infusion is prepared, which is taken, whilst hot, in syphilitic and other disorders. Guaiacum is evidently its chief constituent, and this is the most usual form in which the celebrated Lignum sanctum of Hutten and Cellini is still employed. Sarsaparilla is officinal in the DECOCTUM SARSAPARILLÆ COMPOSITUM, which, according to the directions of the German Pharmacopœia, is prepared by digesting 20 parts of sarsaparilla in 520 of water, and then boiling this with 5 parts of senna leaves, 2 of liquorice root, 1 each of aniseed and fennel fruit, and afterwards adding 1 part of alum and 1 of sugar. Of this the patient drinks from half a litre to a litre (one to two pints) daily, having first warmed it by placing the vessel containing the dose in hot water. This is the modern simplified

[1] Kaposi, 'Verhandl. d. Congresses f. innere Med.,' Wiesbaden, 1886, S. 265.

[2] A. Vesalius, 'Epistola rationem modumque propinandi radicis Chinæ decocti, quo nuper invictissimus Carolus V, Imperator, usus est, pertractans,' &c., Basel, 1546, 4. (The Emperor took it to relieve the gout.)

form of Zittmann's decoction. J. Fr. Zittmann, who lived from 1671 to 1757, was an army surgeon and court physician at Dresden, and his chief writings relate to medical jurisprudence. His receipt for the antisyphilitic mixture was first published by Theden.[1]

[1] Theden, 'Neue Bemerkungen und Erfahrungen,' Berlin, 1771, Bd. ii.

XXII.

The experimental investigations on fermentation and putrefaction, of Th. Schwann, Caignard, and Fr. Schulze—Their successors—The antiseptics included in the Pharmacopœia —Potassium permanganate, chlorinated lime, and others —Inorganic preparations—Potassium chlorate—Carbolic acid and its derivatives—Charcoal.

OUR present knowledge of the changes produced by putrefaction and fermentation is of recent date, notwithstanding the speculative views which for centuries have been put forward, and the experimental investigations which, from time to time, have been made, as to their nature. It was only in 1836 and 1837, by the researches of Fr. Schulze[1] and Th. Schwann[2] in Germany, and of Cagniard-Latour[3] in France, that the matter was placed on a satisfactory basis, and that the investigations were turned in the right direction. The above-mentioned writers were the first to recognise that fermentation and putrefaction[4] were due to the

[1] Fr. Schulze, 'Annal. d. Phys. u. Chem.,' 1836, Bd. xxxix, S. 487.

[2] Th. Schwann, Congress of Naturalists and Physicians at Jena, September, 1836, 'Report in the Isis,' 1837, S. 523; see also "Vorläufige Mitteilung, betr. Versuche über Weingärung und Fäulnis," 'Annal. der Phys. u. Chem.,' 1837, B. xli, S. 184.

[3] Cagniard-Latour, L'Institut. Paris, 23rd November, 1836. Schwann and Cagniard-Latour were unacquainted wtih each other's researches.

[4] Schwann, in the communication referred to above, dated 1837, says:—"The explanation of the putrefactive process is to be found in the fact that as these growths [of mould and of infusoria] are developed and sustained at the expense of the organic substance, they produce such disintegration of the latter, as gives rise to the phenomena of putrefaction. . . . . This at once suggests the idea that possibly vinous fermentation results from the decomposition of sugar, caused by the

presence of the lowest organisms, the yeast and fission fungi (saccharomyces and schizomycetes), and these fundamental facts were subsequently developed by Helmholtz, E. Mitscherlich, Schröder, v. Dusch, and Pasteur. The last from 1857 onwards successfully maintained the correctness of this view against all opponents, and also extended and enlarged it by the addition of fresh facts and experiments.[1]

The aim of antisepsis or antizymosis[2] applied medically, is to prevent, decrease, or put a stop to those processes which depend upon the activity of the yeast and fission fungi, and it consequently acts directly on these organisms. It is immaterial whether the organisms themselves, or the unorganised ferments produced by them are the real decomposing agents. Changes are produced in both ways. Take for instance, the beer yeast (*Saccharomyces cerevisiæ*). It is only the LIVING cells which are capable of decomposing grape-sugar into alcohol and carbonic acid, an effect which neither a glycerine extract nor a watery infusion of yeast can produce. On the other hand, a ferment, or enzyme, which is contained in the aqueous infusion of yeast transforms, with hydration, cane-sugar into invert-sugar, that is, into a mixture of dextrose and levulose: $C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$. As this ferment is produced by the yeast cells—all soluble ferments of the kind being products of living cells—we shall, by paralysing the cell, limit or prevent the development of the soluble ferment. The same holds good with regard to the disinfection of wounds in the human subject, whether the changes in the tissue are caused by bacteria or cocci which are lodging there, or whether they result from a soluble ferment which is produced by these organisms.

development of infusoria, or of some sort of plant. . . . . The connection between vinous fermentation and the sugar fungus [Zuckerpilz is the term Schwann applies to yeast] is therefore not to be mistaken."

[1] Pasteur's first work on fermentation appeared in 1857 ('Compt. rend,' vol. xlv, p. 931). In it, adopting the view of his predecessors, he discusses the fungus upon the presence of which lactic acid fermentation depends; see also C. Ingenkamp, "The History of the Development of our Knowledge regarding Putrefaction and Fermentation," 'Zeitschr. f. klin. Med.,' 1885, Bd. x, S. 59—107.

[2] Σήπω = to decompose; ζυμόω = to ferment.

Antiseptics, consequently, act upon both kinds of ferments, both upon the cells themselves, and upon their soluble products, but, generally, more efficiently upon the former than upon the latter.

It is impossible to give any description of the properties of the various officinal remedies belonging to this class which will be applicable to them all, owing to the great variations in the power of resistance of the various cocci, bacteria, &c., to the action of chemical agents. It may be said that, generally, free chlorine is the most efficient, its effect on the different kinds of organisms having been carefully determined experimentally.[1]

I now proceed to discuss and demonstrate to you the various officinal antiseptics, and will first take the oxidising agents.

KALIUM PERMANGANICUM, potassium permanganate, $KMnO_4$. Dark violet, almost black, slender, prismatic crystals, forming when dissolved in 21 parts of water a deep purple solution. An aqueous solution of 1 in 1000 is neutral to litmus paper, and its colour is discharged by reducing agents. Many substances which are readily oxidised, take fire and explode when rubbed with this salt.

Its solution is sometimes called CHAMELEON SOLUTION, because the red permanganate and the green manganate are readily transformed the one into the other, and then show the colours intermediate to those two. The following experiment illustrates this. To the aqueous solution of permanganate in this test-tube, I add some caustic soda, and then pour some alcohol down the tube, so that it rests on the surface of the liquid. In a few minutes, at the junction of the two layers, and where the alcohol and permanganate are mixed together, a green colour appears, and gradually extends throughout the whole of the contents

[1] C. Binz, "Ueber die Wirkung antiseptischer Stoffe auf Infusorien von Pflanzenjauche," 'Centralbl. f. d. med. Wiss.,' 1867, S. 305; L. Bucholtz, 'Arch. f. exper. Path. u. Pharm.,' 1875, Bd. iv, S. 1; N. J. de la Croix, ibid., 1881, Bd. xiii, S. 175; A. Krajewski, ibid., 1881, Bd. xiv, S. 138; H. Schmidt-Rimpler, 'Arch. f. path. Anat.,' 1877, Bd. lxx, S. 1; R. Koch, in dem 'Mitteil. a. d. Kaiserl. Gesundheitsamte' from 1881 onwards; wherein he also describes new methods of research, by which every department of the subject has been enriched.

of the tube. A brown precipitate at the same time falls to the bottom of the tube. The change is represented by the following formula:

$$2KMnO_4 = K_2MnO_4 + MnO_2 + 2O.$$

That is to say, the permanganate, in the presence of an alkali and an oxidisable body, parts with half its oxygen, and is transformed into peroxide of manganese, MnO_2, which is precipitated, and into the green manganate, K_2MnO_4, the alcohol being transformed at the same time, by the liberated oxygen, into acetic acid, &c.

If I now dissolve the dark green potassium manganate, obtained by fusion, in some warm water, the colour quickly changes into blue, violet, and deep purple, hydrated manganic dioxide being formed, which subsides, and potassium permanganate, which remains in solution, together with a small amount of potassium hydrate. The manganate is decomposed by the water, and the following change takes place:

$$3K_2MnO_4 + 3H_2O = 2KMnO_4 + MnH_2O_3 + 4KOH.$$

The antiseptic or disinfecting action of the permanganate is due to the ready way in which it yields its oxygen, in a nascent form, to oxidisable substances. This flask contains some pus mixed with water, the odour of which is somewhat offensive. I add to it a solution of the permanganate, and the colour of the mixture at once becomes brown from the formation of the lower oxides of manganese; the offensive odour is lessened or entirely removed, and in its place, if the solution of permanganate was strong enough, we notice the peculiar odour of ozone, that is, of nascent or active oxygen.

If I place a drop of sediment teeming with putrefactive organisms under the microscope, and add a drop of the permanganate solution, we see that every living and moving organism very quickly dies and becomes black and shrivelled. Protoplasm possesses marked reducing properties, and, following the law of other bodies in this respect, is oxidised by the permanganate. The action ceases so soon as the latter substance has given up all its available oxygen.

In 1859 A. W. Hoffmann was the first to recommend the use of potassium permanganate as a disinfectant.

Morphine is very readily oxidised by potassium permanganate. If I mix solutions of these two substances together

in a test-tube, you see that in a few seconds the beautiful purple colour is replaced by a brown colour, owing to the reduction of the permanganate and the partial oxidation of the morphine. This has led to the employment of the permanganate as an antidote in cases of morphine poisoning, with the object of oxidising any portion of the latter which may be in the stomach. W. Moor took 0·18 gramme (2¾ grains) of morphine sulphate, or eighteen times the quantity necessary to induce sleep, and immediately afterwards a solution containing 0·24 gramme (3½ grains) of potassium permanganate. No soporific effect was produced by the morphine.[1] Raw treated five cases of morphine poisoning with this remedy, four of which recovered.[2] The other was dying when first brought under observation. The remedy was administered by means of the œsophageal tube. As morphine when circulating in the blood is, to a large extent, excreted by the mucous membrane of the stomach (see Vol. I, p. 66), this method of treating persons under the influence of the drug may be attended with satisfactory results.

The administration for a lengthened period of potassium permanganate, in doses of 0·1 gramme (1½ grains) two or three times a day, has been recommended by English physicians in cases of defective menstruation. It is stated that abortion may result from its use.[3]

Calcaria Chlorata, Calx Chlorinata, chlorinated lime, or bleaching powder, is a dull white powder, with an odour similar to that of chlorine, but not so pungent, and a slightly sweet taste. It is partially soluble in water, and has an alkaline reaction. Chlorinated lime should contain at least 20 per cent.[4] of available chlorine; that is to say, of chlorine in such loose combination that it is readily given up to reducing agents.

Chlorinated lime is obtained by exposing slaked lime to the action of chlorine gas as long as the latter is absorbed.

[1] W. Moor, 'Brit. Med. Journ.,' June 22nd, 1895.
[2] N. Raw, ibid., July 13th, 1895.
[3] 'Wien. med. Wochenschr.,' 1888, S. 839.
[4] According to the British Pharmacopœia, 33 per cent. (transl.).

There are three different views as to its chemical constitution,[1] which are as follows:

$$\text{I.—}Ca(OCl)_2 + CaCl_2.$$
$$\text{II.—}CaCl.OCl.$$
$$\text{III.—}Ca(OCl)_2 + Ca(OH)_2.$$

Which is the correct one, still remains undetermined. The chief point, as far as we are concerned, is that according to either formula, hypochlorous acid is liberated by the action of free acids, and even by carbonic acid. Taking the second formula, for example, we have with carbonic acid—

$$2CaCl.OCl + H_2O + CO_2 = CaCO_3 + CaCl_2 + 2ClOH.$$

The last, the hypochlorous acid, to which the peculiar odour of chlorinated lime is due, is very quickly decomposed, even at the ordinary temperature, chiefly as follows:

$$2ClOH = H_2O + 2Cl + O.$$

Similar changes, of course, are produced by the action of stronger acids. We have, for instance, by the action of dilute sulphuric acid—

$$2CaCl.OCl + H_2SO_4 = CaCl_2 + CaSO_4 + 2ClOH.$$

On adding twice the quantity of sulphuric acid no hypochlorous acid is evolved, but simply chlorine—

$$2CaCl.OCl + 2H_2SO_4 = 2CaSO_4 + 2H_2O + 4Cl.$$

Chorinated lime is consequently chlorine in an easily portable form, and, if the evolution of active or nascent oxygen is taken into account, may also be regarded as a source from which that powerful antiseptic may be obtained. These facts fully explain all that experience has taught us with regard to the destructive action of this compound on the lowest forms of organised life. It is necessary, however, in using the commercial product, especially when obtained in large quantities, to note the quantity of available chlorine which it contains. Even by exposure to the air its activity is lessened, as the above formula shows, calcium carbonate being formed and hypochlorous acid liberated, and gradually the preparation becomes worthless. The Pharmacopœia gives a method of titration by means of which the amount of available chlorine in a specimen can readily be determined.

Chlorine is the most effective of all antiparasitic remedies,

[1] F. Kopfer, 'Ann. d. Chemie,' 1875, Bd. clxxvii, S. 314; Stahlschmidt, Dingler's 'Polyt. Journ.,' 1876, Bd. ccxxi, S. 243.

for by it the infective power of anthrax spores, the vitality and power of resistance of which are greater than those of any other organism, is destroyed in a few seconds.[1]

The following is a convenient way (suggested by Geppert) of disinfecting the hands by chlorine:—A moderately soft paste is prepared by mixing the chlorinated lime with water, and then passing it through a hair sieve. After rubbing this over the hands, the latter are dipped into a 1 or 2 per cent. solution of hydrochloric acid, prepared by mixing 50 to 70 c.cm. of the officinal hydrochloric acid with a litre of water (3 to 5 drachms of the acid to a quart of water).

Cases of POISONING by the exhalations from chlorinated lime have occasionally been reported. Poisonous effects, however, are produced more frequently by two other analogous preparations, which are used for laundry purposes, namely, Labarraque's and Javelle's solutions. The first contains potassium hypochlorite, $KOCl$; the latter, sodium hypochlorite, $NaOCl$, together with potassium chloride and sodium chloride; and both are prepared by passing chlorine into solutions of the carbonates of the respective alkalies. The symptoms of poisoning by these preparations are localised irritation and erosion of the alimentary canal, and paralysis of the nervous centres.[2] Of course, when the hypochlorous acid is liberated, it is at once decomposed in the way I have already mentioned. It is very remarkable for what a length of time, comparatively, the liberated chlorine remains in the system.

The treatment suitable in such cases is to endeavour to sustain the nervous energy and the bodily temperature, and by means of albuminous and mucilaginous drinks to diminish the intestinal irritation.

BROMUM, bromine, the well-known element, produces similar effects to those of chlorine, and is used for similar purposes. It is a dark brown, very volatile liquid, having a sp. gr. of about 3. At the ordinary temperature of

[1] J. Geppert, "Zur Lehre von den Antisepticis," 'Berl. klin. Wochenschr.,' 1889, No. 36; "Ueber desinficirende Mittel und Methoden," ibid., 1890, No. 11.

[2] See the cases of Simonson and Cameron, quoted by me in the 'Arch. f. exper. Path. u. Pharm.,' 1880, Bd. xiii, S. 151.

the air it gives off red vapours having a strong and disagreeable odour. It is readily soluble in alcohol, ether, and chloroform, and in 30 parts of water.[1] It has a distinctly poisonous action on the lower organisms, and on this account its use has been recommended as an inhalation in cases of diphtheria, 4 parts being dissolved in 200 of water, and the spray from this inhaled three or four times a day. It may be used in other ways and for various purposes by patients who do not object to its disagreeable odour.

The poisoning effects of bromine are very similar to those resulting from chlorine or chlorinated lime.

The three preceding antiseptics form a natural group, acting as they do in the same way, namely, by oxidising disease germs, and so inhibiting or destroying them. With regard to the following compounds, their mode of action, from a chemical point of view, is not very clear. I will take first of all, as having, possibly, an action similar to the preceding antiseptics,—

Acidum Boricum, boric acid, H_3BO_3. The crystals of this are colourless, pearly, lamellar, and unctuous to the touch. They have a feebly acid and bitter taste, and leave a sweetish after-flavour in the mouth. They are soluble in 25 parts of cold and 3 of boiling water, in 16 parts of rectified spirit, and 5 of glycerine. The crystals liquefy when warmed, and solidify on cooling to a brittle glass-like mass. The watery solution, slightly acidified with hydrochloric acid, causes the colour of turmeric paper to become brown. The alcoholic solution burns with a flame tinged with green.

Homberg, in 1702, obtained boracic acid by heating ferrous sulphate with sodium biborate (borax), and introduced it as a medicinal agent under the name of *Sal sedativum*.

It was subsequently discovered to be a free acid, not a salt. It was administered internally as a remedy until Binswanger,[2] in 1847, after making careful experiments with

[1] Wernich, 'Centralbl. f. d. med. Wiss.,' 1882, S. 180; Dolleschall und Frank, 'Deutsche med. Wochenschr.,' 1881, S. 180; B. Fischer u. Proskauer, 'Mitteil. a. d. Kaiserl. Gesundheitsamte,' 1884, Bd. ii, S. 280. (Same date, p. 229, 'Ueber den Desinfectionswert von Chlorgas.')

[2] L. Binswanger, 'Pharmakologische Würdigung des Borsäure,' u. s. w., München, 1847.

it, came to the conclusion that when given in medicinal doses it had no effect on the organism, and should not be employed therapeutically. This investigator, in the course of his experiments, took on one day, within an hour, 7·5 grammes (115 grains) of boracic acid, and a few hours later took half that amount. The only results worth mentioning, were disturbed digestion, vomiting of the contents of the stomach, which were highly alkaline, together with frequent and urgent urination, the amount passed in the subsequent twenty-four hours being increased to the extent of one third.

Dumas, the distinguished chemist, in 1872 discovered the antiseptic properties[1] of boracic acid, and soon afterwards it was employed as a dressing by Lister. Other substances act more energetically, but boracic acid possesses this advantage, that it produces little or no irritation of the tissues to which it is applied. It has also another valuable property, dependent upon its action on the lower organisms, namely, that when applied locally it checks suppuration;[2] it does so by immediately paralysing the white blood-corpuscles as they emerge through the vascular walls, and without in any way irritating the inflamed tissue.

BORAX, sodium biborate, the salt of boracic acid, has continuously held its place as a useful remedy. It consists of hard, colourless, prismatic crystals, or of crystalline masses, which require seventeen parts of cold and half their weight of boiling water for solution. Borax readily dissolves in glycerine, but is insoluble in rectified spirit. Its solutions have an alkaline reaction to test-paper, and have also a faintly alkaline taste. Its composition is $Na_2B_4O_7 + 10H_2O$, the first being formed as follows:

$$4H_3BO_3 + Na_2CO_3 = Na_2B_4O_7 + CO_2 + 6H_2O.$$

In former times various healing properties were assigned to borax, but we hear little of them at the present day.

[1] Dumas, 'Comptes rendus de l'Acad. des Sc.,' Paris, 1872, vol. lxxv, p. 295; J. Neumann, 'Arch. f. exper. Path. u. Pharm.,' 1881, Bd. xiv, S. 149.

[2] F. Kurz, 'Memorabilien f. prakt. Aerzte,' 1862, S. 515; Walb, 'Centralbl. f. klin. Med.,' 1882, S. 529.

Binswanger took 18·75 grammes (290 grains) within three hours, the only effects produced being vomiting and diarrhœa. A certain number of practitioners at the present day consider that it promotes the menstrual flow; a smaller number believe that it has ecbolic properties.

The value of borax when employed as a lotion, fomentation, or injection, in various disorders of the skin and mucous membranes, has not been denied. It was generally regarded as having a slightly astringent effect in these cases, until its strong antizymotic action was discovered.[1] Borax prevents the enzyme dissolved in the fluid medium of yeast from transforming cane-sugar into invert-sugar, and checks the fermentative action of emulsion upon amygdaline, of diastase on sugar, and of myrosine on myronic acid (contained in black mustard seeds). It also has a destructive action on various kinds of protoplasm, and, very probably in this way, prevents animal tissues from putrefying, the development of the putrefactive bacteria being stopped.

It is probably due to the alkaline reaction of the borates, that they have been generally employed, since the time of Paracelsus, as remedies for all forms of uric acid deposits in the kidneys and in the bladder.

Boracic acid is employed as a preservative for various articles of diet, and their digestibility may be thereby affected. A pupil of Forster[2] took daily with his food 3 grammes (46 grains), and this was followed by disturbed digestion. In cases of dyspepsia it is well for physicians to bear in mind the possibility of the disorder arising from this cause.

There remain for consideration two salts of aluminium; the first aluminium acetate, which is officinal as LIQUOR ALUMINII ACETICI, solution of acetate of aluminium, practically $Al_2(OH)_2.(C_2H_3O_2)_4$. It is prepared by mixing together a solution of aluminium sulphate with dilute acetic acid, and precipitating the sulphuric acid by means of calcium carbonate.

[1] Dumas, a. a. O.; J. B. Schnetzler, 'Ann. chim. et phys.,' 1875, Bd. iv, S. 543; E. de Cyon, 'Compt. rend. Acad. des. Sc.,' 1878, vol. lxxxvii, p. 845.

[2] J. Forster, 'Arch. f. Hygiene,' 1883, Bd. ii, S. 75. Compare with this the views of O. Liebreich, 'Therap. Monatsh.,' 1887, S. 353.

It is a clear, colourless liquid, with a faint acetous odour, and has an acid reaction and a sweetish astringent taste. The salt itself does not crystallise, and is very deliquescent. The officinal solution has a sp. gr. of 1·045. It is neither an irritant nor a poison, but is strongly antiseptic. The Aluminium Sulphuricum, $Al_2(SO_4)_3 + 18Aq.$, which is used in the preparation of the above solution, consists of crystalline masses which are soluble in an equal weight of water, and have an acid reaction and an astringent taste.

This salt, as well as alum, which I shall discuss presently, and aluminium oxyhydrate, possesses the property of absorbing and fixing various organic substances, especially odorous and colouring matters. This led to the discovery by Reich, the chemist, of the active power which the acetate possesses in preventing putrefactive changes.

The sugar manufacturers added it to the blood which they use as a clarifying medium, and in this way the attention of Burow, a surgeon in Konigsberg, was directed to the compound.[1] Its effect on albumen is also noteworthy. If fresh albumen is incorporated with one third to one fourth its weight of aluminium acetate, it is converted into a limpid fluid almost like water, which remains quite clear. On boiling, the mixture coagulates less easily, and at a somewhat higher temperature, than simple albumen. Coagulated albumen is slightly soluble in aluminium acetate. Burow recommends the use of this remedy in many external affections, particularly in those which are accompanied by suppuration or by an offensive odour. A solution in water (1 in 4) may be dropped into the ear in cases of furunculosis of that organ.[2] He also recommended its employment for the preservation of corpses; it can be readily distributed throughout the body by injecting it into one of the large arteries.

He tried upon himself its effects when taken internally. Whilst fasting he took thirty drops of a solution having a sp. gr. of 1·039, and experienced simply a feeling of warmth and fulness. After taking sixty drops both these sensations were increased, and he was seized with giddiness

[1] Burow, 'Deutsche Klinik,' Berlin, 1857, S. 147 und 155.

[2] Grosch, 'Berl. klin. Wochenschr.,' 1888, No. 18.

and stupor, which lasted some time. Its use has been strongly recommended in enteritis affecting children.[1]

The other aluminium salt is ALUMEN, potash alum, sulphate of aluminium and potassium, the composition of which is—

$$Al_2K_2(SO_4)_4 + 24H_2O.$$

It consists of colourless, transparent crystals or crystalline masses, exhibiting the faces of the regular octahedron, and efflorescing superficially. It is soluble in eleven parts of water, but insoluble in rectified spirit; its aqueous solution has an acid reaction, and a sweetish, strongly astringent taste. Alum precipitates albumen. On this account, probably, it is sometimes used in the proportion of 1 to 3 grammes to 10 litres (15 to 46 grains to 18 pints) to purify water. Any organisms which may be present in the water are thereby paralysed and destroyed. Internally it is employed in doses of 0·1 to 0·3 gramme (1½ to 4½ grains) given as a powder, in hæmorrhage from the intestinal canal, and in cases of diarrhœa. In the latter, its antiseptic in addition to its astringent properties may not unfrequently be useful; this may also be the case when it is applied locally to mucous membranes. If administered internally in too large a dose, it may set up inflammation of the stomach and intestines.

Wibmer took 3·6 grammes of alum dissolved in 0·5 litre of water (55 grains in 18 ounces) in the course of two days. His appetite and digestion were undisturbed, there was no increase of thirst, but the bowels became unusually constipated. On discontinuing the alum on the third day, diarrhœa supervened.

ALUMEN USTUM, dried alum, is prepared by carefully heating the previous salt at a temperature not exceeding 204° C. (400° F.), so as not to liberate any sulphuric acid, but to deprive it of the greater part of its water of crystallisation. It is a white powder, slowly soluble in water, and has a styptic taste. Being deprived of its water of crystallisation, dried alum acts slightly as a caustic. It is applied in the form of a powder to discharging surfaces.

If alum is mixed with a solution of sodium carbonate we

[1] Soltmann, 'Forty-eighth Report of the Wilhelm-Augusta Hospital,' Breslau, 1886.

obtain a precipitate of ALUMINA HYDRATA, aluminium hydrate, which was formerly officinal. It is a flocculent, white, tasteless mass, which adheres to the tongue, and is insoluble in water. It is slowly dissolved by acids, but does not neutralise them. When freshly precipitated, aluminium hydrate has a very powerful attraction for odorous and colouring matters. Here I have a specimen of decomposing offensive blood, to which I add a sufficient quantity of the hydrate, and mix them well together. In a few minutes the offensive odour will have disappeared. Possibly the constipating action of aluminium hydrate, for which purpose it was formerly much employed, depends upon its combining in the intestines with gases which are causing irritation there. It is administered in doses of 0·1 to 1·0 gramme (1½ to 15 grains) in the summer diarrhœa of children, and in chronic diarrhœa of adults.

BOLUS ALBA, argilla, consists of aluminium silicate, $Al_4Si_3O_{12} + 4H_2O$, contaminated with some immaterial substances. It is also known as porcelain clay or kaolin, and is a white friable mass which forms with water a somewhat stiff paste, but does not dissolve in that liquid. It must be free from chalk and sand, and must therefore not effervesce when mixed with hydrochloric acid, and when washed with water must leave no sandy residue. Being a neutral substance which is not easily decomposed, it is consequently used medicinally, but chiefly as an external remedy. It is employed as a dusting powder to discharging surfaces, as an injection (5 parts to 200 of water) in gonorrhœa, and as a vehicle for the administration, in the form of pills, of substances which are easily decomposed, such as nitrate of silver and corrosive sublimate.

FERRUM SULPHURICUM CRUDUM, ferrous sulphate (see page 42, Vol. II), is also employed as a disinfectant. It consists of crystals or crystalline masses, having a green colour, generally slightly damp, more rarely coated with a fine white powder, forming when dissolved in 2 parts of water a slightly turbid solution, which has an acid reaction and a styptic, ink-like taste.

It is largely used to disinfect privies, cesspools, and sewers, and acts by converting the poisonous gases, sul-

phuretted hydrogen and ammonium sulphide, into ferrous sulphide; and also when added in sufficient quantity makes the liquid acid and consequently destructive to many kinds of bacilli. If I am not mistaken, Pettenkofer, during a cholera epidemic upwards of thirty-six years ago, recommended ferrous sulphate as one of the cheapest disinfectants. That his view of its action was correct is shown by the researches of R. Koch, which prove that the bacillus of Asiatic cholera is very readily affected by acid liquids. Consequently when the quantity of the salt employed is proproportionate to the liquid or sediment to be disinfected, good results may be expected from its use.

Among antiseptic remedies special consideration must be given to—

KALIUM CHLORICUM, Potassii Chloras, potassium chlorate, $KClO_3$. It consists of colourless rhomboidal crystalline plates, which have a slightly saline taste and are unaffected by exposure to the air. The salt is soluble in 16 parts of cold and 3 parts of boiling water, and 130 parts of rectified spirit. The solutions are neutral to test-paper.

Potassium chlorate is not an antiseptic in the ordinary sense of the term, for outside the human body it produces very little effect even upon bacteria which are very sensitive to other agents;[1] but under certain conditions it acts as an antiseptic IN THE LIVING TISSUES of the human subject. In the putrid stomatitis of scorbutic or mercurial origin, and in similar affections of other mucous membranes, we have evidence of this action.

It was first employed as a remedy entirely on theoretical grounds. Lavoisier enabled us clearly to understand the nature of combustion, and thereby laid the foundation upon which our knowledge of the respiratory changes is based.

[1] Kitasato und Weyl, 'Zeitschr. f. Hygiene,' 1890, Bd. ix, S. 100.

It was afterwards assumed that the salts of nitric and chloric acids parted with their oxygen in the system, and this was supposed to be the case especially with regard to the chlorates, as they are completely reduced when heated; potassium chlorate being reduced, for instance, to potassium chloride, and free oxygen being liberated:

$$KClO_3 = KCl + 3O.$$

Consequently at the end of last century potassium chlorate was employed, and its use highly recommended in the most diverse disorders.[1] Time, however, has failed to bring about any confirmation of these statements and results, and it was only in 1840 that Böckh of Greifenhagen assigned to the salt its proper place in therapeutics.[2] He reported very favourably of its action in those cases of profuse salivation, associated with ulceration of the mucous membrane of the mouth, which sometimes occur in typhoid fever after large doses of calomel. Subsequently to his report, all forms of ulcerative disorder of the mouth were treated with this drug.

Numerous scientific investigations of the action of this new remedy were then undertaken. Wöhler[3] gave 3·6 grammes of it, and shortly afterwards detected its presence in the urine. The only effects produced on the animal were diarrhœa and increased urination. A few years later O'Shaughnessy noticed much the same results, and since 1853 the action of the drug has been exhaustively investigated, especially by Isambert of Paris. For several days in succession he took 8 to 20 grammes (2 to 5 drachms) with his food; the effects produced were simply increased flow of saliva which had a saline taste, increase of appetite, increased flow of urine, and some heaviness and pain in the region of the kidneys. Subsequently he investigated the mode of elimination of the salt, and his opinion was that it passed through the system entirely unchanged.[4]

[1] M. Tacke, 'Das chlorsaure Kali in medicinischer Hinsicht,' Doctor-dissert., Bonn, 1878; J. v. Mering, 'Das chlorsaure Kali, seine physiol. tox. u. therapeut. Wirkungen,' Berlin, 1885.

[2] Böckh, 'Med. Centralzeitung,' Berlin, 1840, S. 113.

[3] Wöhler, 'Zeitschr. f. Physiol.,' 1824, Bd. i, S. 131.

[4] Isambert, "Nouvelles expér. sur l'action physiol., tox., et thérap.

As the result of these investigations, the view that the remedy acted by furnishing oxygen to the tissues was entirely abandoned. The idea had been, that the salt acted as if heated in a chemical retort, by giving off the whole of its oxygen; but observers now fell into the opposite error, and denied that it was decomposed in any way, either in the blood or the tissues. They were content with asserting that the beneficial effects, which the remedy unquestionably produced, were not capable of explanation, or they referred them to some stimulation of the vaso-motor system, without advancing the smallest particle of evidence in proof of their assertions.

I now commenced some investigations in order to determine how far putrid albuminous substance could abstract oxygen from potassium chlorate.[1] That organic bodies in the dry state would do this and cause an explosion was well known; but that the oxygen could be abstracted by an aqueous solution, and without heating the latter, had not been demonstrated. The following are the details of one of my experiments.

Some fibrin was obtained from bullock's blood. About 0·15 gramme of this was minutely divided and placed in 75 c.c. of an aqueous solution (1 to 2000) of potassium chlorate, the mixture was rendered slightly alkaline with solution of soda, and then kept at a temperature ranging between 25° and 40° C. In a few days it was intensely putrid and swarming with bacteria. I now tested for the presence of chloric acid in the following manner. About 1 c.c. of the mixture was put into a test-tube, with a few drops of starch mucilage and a few drops of a dilute solution of potassium iodide. To this an equal volume of strong hydrochloric acid was added. The test was so devised as to detect the presence of potassium chlorate in a solution, even when diluted with water to the extent of 1 in 50,000, by the development of a blue colour. This results, as is well

du chlorate de potasse," 'Gaz. méd. de Paris,' 1875, pp. 199, 432, 510, 537.

[1] C. Binz, "Sitzungsber. d. Niederrhein Gesellsch. f. Natur- u. Heilk." vom 19 Mai, 1873, ref. 'Berl. klin. Wochenschr.,' 1874, S. 119; 'Arch. f. exper. Path. u. Pharm.,' 1878, Bd. x, S. 153.

known, from potassium chlorate being decomposed when hydrochloric acid is added to it, chlorine being liberated, as you see from the following formula :

$$KClO_3 + 6HCl = 3H_2O + KCl + 6Cl.$$

The chlorine then acts upon the potassium iodide and liberates the iodine, which gives a blue colour with the starch. The putrid mixture above mentioned, shortly after the addition of the potassium chlorate, showed the blue reaction very distinctly, but at the end of fourteen days no trace of the reaction could be seen, even after the test had been applied for several hours.

As the result of this experiment, it appeared to me that in the various kinds of putrid inflammation of the mouth and throat, and also in catarrh of the bladder with decomposition of the urine, the beneficial effects are produced as follows: —Potassium chlorate contains 39 per cent. of oxygen, which is easily liberated from it. The chlorate is continuously eliminated by the salivary glands, the mucous membranes, and the kidneys. If it comes in contact with septic tissue, this reduces it to potassium chloride, KCl. The three atoms of oxygen which are liberated are in the nascent state; they consequently continuously stimulate the tissue, the effect of which may be compared to that of a gentle irritant or caustic, and approaches that resulting from the action of largely diluted solutions of nitrate of silver, chlorinated lime, and similar substances. This holds good still more when strong solutions of the chlorate are applied locally, either as gargles or with a brush. My experiments—and their significance from a therapeutic point of view—were subsequently further elaborated by the researches of Marchand upon the poisonous action of potassium chlorate. Von Mering has recently confirmed the most important result at which I arrived, namely, that potassium chlorate is reduced by decomposing fibrin.[1]

Finally, the assumption that potassium chlorate passes absolutely unchanged through the organism was shown to be incorrect, by experiments on living animals. From the results of a series of experiments on a dog, Gaehtgens[2] arrived at the conclusion that in the organism a considerable portion

[1] v. Mering, op. cit., Versuche 116—119, S. 129.

[2] Gaehtgens, 'Berl. klin. Wochenschr.,' 1883, S. 386.

of this salt (from one fifth to one fourth of the amount taken, the precise amount reduced being 2 grammes in twenty-four hours) undergoes reduction. This result has also been confirmed and amplified by v. Mering in his exhaustive monograph. The loss which occurs in the amount of this salt, as it passes through the system, is certainly not very great, but it is sufficient, especially when we consider the amount of gas which may be liberated from it, to explain very satisfactorily its therapeutic effects. Further on we shall see that the poisonous effects also, which are produced under certain conditions by the salt, leave absolutely no room to doubt that it gives off oxygen in the organism, and thereby promotes the oxidation of the tissues.

The following experiment shows how rapidly the salt is eliminated from the system through the mucous membranes in addition to being eliminated, as other experimenters have demonstrated, by the saliva, the urine, &c.

My pupil M. Tacke injected 1·5 grammes of sodium chlorate, dissolved in 40 grammes of water, into the stomach of a medium-sized dog. After thirty minutes a feather was passed through an opening in the trachea into the bronchus, rotated a few times, withdrawn, and then washed in water. On testing this, the presence of a chlorate was very clearly demonstrated.

The POISONOUS EFFECTS of potassium chlorate, when given in excessive doses, have frequently been referred to in the medical journals, but very little attention has been paid to these reports. As far as I am aware, the earliest account of these poisonous effects is to be found in a monograph by Isambert in 1856. In 1860, A. Jacobi[1] pointed out the great risk of inducing hæmorrhagic nephritis by large doses. In 1861 Dr. E. J. Fountain, a North American physician, whilst experimenting upon himself with this drug, was poisoned by it. He took two doses of 15 grammes (230

[1] A. Jacobi, 'A Treatise on Diphtheria,' New York, 1880, S. 162. See also reports of thirty-one cases collected by J. Hofmeier und H. Wegscheider, 'Deutsche med. Wochenschr.,' 1880, S. 505, 517, 533; J. Hofmeier, 'Berl. klin. Wochenschr.,' 1880, S. 699; L. Riess, ibid., 1882, S. 785; Wilke, ibid., 1885, S. 251; H. Lenhartz, 'Deutsche med. Wochenschr.,' 1887, S. 9.

grains) in warm water, with only a short interval between them; he was violently purged, the urine became bloody and was then suppressed; there was severe pain in the intestines, followed by vomiting and exhaustion, and death took place seven days after taking the drug. On post-mortem examination it was found that inflammation had been set up in the stomach, intestines, bladder, and kidneys. Other cases in subsequent years were reported, but no light was thrown upon the way in which the fatal effects were produced. Investigators were altogether led astray from rightly interpreting the facts, by the hypothesis that potassium chlorate passed entirely unchanged through the system.

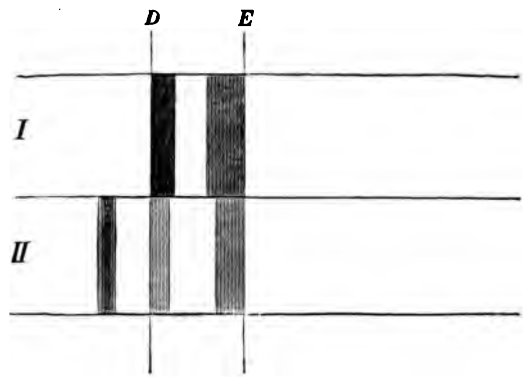
In my laboratory Tacke gave to a rabbit, weighing 1140 grammes, 5·8 grammes of sodium chlorate dissolved in 35 grammes of water. It died four hours afterwards from paralysis of the respiration, and with general convulsions. We were much struck by the *brown* discoloration of the blood, the appearance of which is mentioned in the short account [1] of the post-mortem examination, but circumstances prevented us from further investigating the point, or from repeating the experiment with this object in view. Soon afterwards Marchand [2] was led by certain clinical observations, to make an accurate investigation of the point. He had to make the post-mortem examinations of some individuals who died apparently from diphtheria, after being treated with potassium chlorate. There was a brown discoloration of the blood of these persons, and also of the kidneys, the tubules of the latter being almost entirely blocked with brown-coloured casts. As a result of these observations he endeavoured to produce the same condition in dogs, and was successful in doing so.

The DEGENERATION OF THE BLOOD is caused by the chloric

[1] See Tacke's 'Dissertation,' 1878, p. 58.

[2] F. Marchand, 'Arch. f. path. Anat.,' 1879, Bd. lxxvii, S. 455; 'Arch. f. exper. Path. u. Pharm.,' 1886, Bd. xxii, S. 201 und 1887, Bd. xxiii, S. 273. (A refutation of the statements of J. Stokvis, who from the results of his experiments had arrived at the conclusion that the action of potassium chlorate was simply due to the potassium, and that the chloric acid produced no material effect.) 'Arch. f. path. Anat.,' 1891, Bd. cxiii, S. 577; Lebedeff, ibid., 1883, Bd. xci, S. 274; F. Marchand, 'Deutsche med. Wochenschr.,' 1887, S. 959.

acid, that is to say by the oxygen liberated from the chlorate, and is proximately due to the conversion of the oxyhæmoglobin into methæmoglobin. This change may easily be effected outside the body, by digesting blood for a short time with a chlorate. I here show you such a mixture. If the brown colour were less marked, it might readily be mistaken for the ordinary colour of venous blood; but it is distinguished from the latter by the fact that if we strongly agitate this brown blood with air, the colour does not change to that of arterial blood. By means of the spectroscope you observe, in addition to the two dark bands in the spectrum of oxyhæmoglobin (which, however, are fainter than under normal conditions), a narrower band in the red end. It is situated a little more to the right than



that of hæmatin, in the red part of the spectrum, which we get on the addition of an acid. The most accurate comparison of the two spectra may be made by means of the apparatus devised by Hugo Schulz.[1] If a large amount of oxyhæmoglobin is present, the dark band in the red end of the spectrum may be altogether absent, even though the brown colour of the blood is quite apparent to the naked eye; in this case the blood must be largely diluted.

The same tinge of colour is produced if we mix arterial blood, or still better a solution of pure oxyhæmoglobin in water, with any other oxidising agent, such as potassium

[1] Hugo Schulz, 'Arch. f. d. ges. Physiol.,' 1882, Bd. xxviii, S. 219.

permanganate or nitrate, the nitrites of chlorine, bromine, or iodine. If too large a quantity is added, the desired result is not produced; the methæmoglobin assumes a dirty green colour, and neither its spectrum nor that of oxyhæmoglobin can be obtained.

If the oxyhæmoglobin is entirely transformed into methæmoglobin, we cannot then extract any oxygen from the blood, and blood of this kind no longer suffices for "internal respiration,"—that is to say, it no longer furnishes oxygen to the tissues.[1]

When mixed with ammonium sulphide or any other reducing agent, methæmoglobin is converted into hæmoglobin, and on agitating this with air it is reconverted into oxyhæmoglobin. Formerly it was supposed by some that methæmoglobin was produced by the oxidation of hæmoglobin, by others it was regarded as a product of the latter's reduction. If, consequently, we assume that the molecule hæmoglobin which gives rise to Stokes's band in the spectrum is Hb, and oxyhæmoglobin HbO_2, then methæmoglobin must be either HbO_3 or HbO. According to the most recent, and probably also the most exact experimental investigations,[2] neither of these views is correct; but it is asserted that methæmoglobin is isomeric with oxyhæmoglobin, HbO_2, and has its oxygen so strongly combined with the hæmoglobin that they cannot be separated by the usual methods.

The alkalinity of the blood is diminished; after death it has been found to have an acid reaction. The red corpuscles even during life undergo partial disintegration; their colouring matter appears, both within the stroma and external to it in the serum, as small round granules, the colour being still retained.

The altered form of the red blood-corpuscles does not depend upon the methæmoglobin, for the amount of this may

[1] On this consult Hoppe-Seyler, 'Zeitschr. f. physiol. Chemie,' 1878, Bd. ii, S. 150, and 1882, Bd. vi, S. 166; L. Saarbach, 'Arch. f. d. ges. Physiol.,' 1882, Bd. xxviii, S. 382; G. Hüfner und R. Külz, 'Zeitschr. f. physiol. Chemie,' 1883, Bd. vii, S. 366; J. Otto, 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxxi, S. 245; A. Jäderholm, 'Zeitschr. f. Biologie,' 1884, Bd. xx, S. 419; 1880, Bd. xvi, S. 1; 1877, Bd. xiii, S. 193.

[2] P. Dittrich, 'Arch. f. exper. Path. u. Pharm.,' 1891, Bd. xxix, S. 247.

From a drawing by L. Riess.

be very considerable, even when very little disintegration of the corpuscles has taken place.[1]

Blocking of the renal tubules is another effect resulting from large doses of potassium chlorate. There is no change, at least no primary change, observable in the parenchyma of the kidney. The tubules are blocked by the altered blood, that is by the disintegrated blood-corpuscles. These form brownish casts which are composed of minute spheres and granules.

The symptoms of poisoning by potassium chlorate are as follows:—There is a cyanotic condition of the skin, which is induced by the methæmoglobin, and may be distinguished from that due to suffocation, by the fact that a drop of blood taken from the finger and spread out on a white surface does not assume a bright arterial red colour, but retains its brown appearance. Further, there is jaundice, dependent probably on swelling of the mucous membrane of the larger bile-ducts; vomiting of blood, which has an abnormal appearance; violent purging; enlargement of the liver and spleen; uræmic symptoms, such as delirium, stupor, coma, and convulsive movements. These may be the result of the direct action of the chlorate on the brain,[2] and certainly are the result of its action on the kidneys.

Owing to the blocking of the renal tubules the urine is scanty, and is often entirely suppressed. Its colour is reddish brown, sometimes almost black; it is highly albuminous, and loaded with the detritus of the red blood-corpuscles, in the form of casts and granular masses.

As an explanation of the way in which death is brought

[1] A. Lesser, 'Atlas der gerichtl. Med.,' 1883, S. 149.

[2] L. Riess, 'Centralb. f. Physiol.,' 1887, No. 10.

about, it has been suggested that, owing to the formation of methæmoglobin, the blood is unable to absorb and act as the carrier of oxygen, and that consequently local or internal asphyxia of the organs is produced. This may be the case when there is extensive degeneration of the blood, but it has been demonstrated, both experimentally and in various instances which have occurred,[1] that if the degeneration takes place to a moderate extent only, no injury results therefrom. Five grammes of sodium chlorate were injected directly into the vein of a dog weighing 10 kilogrammes. Five hours later the dog, which apparently was perfectly well and did not exhibit the slightest want of breath, was bled to death. The blood was of a dark brown colour, and on spectral analysis showed, in addition to the two dark bands of oxyhæmoglobin, the dark band in the red portion of the spectrum.

I may add, by the way, that in this instance the quantitative analysis of the blood showed that each 10 c.c. had, in the course of five hours, reduced 0·013 gramme of sodium chlorate.

As it formerly happened that, in many cases of poisoning from potassium chlorate, the symptoms were erroneously supposed to be due to diphtheria, so, on the other hand, in fatal cases of diphtheria, the symptoms may be very easily mistaken for those of poisoning from the chlorate. In fact, it may undoubtedly happen that symptoms of poisoning of a slight but not fatal character may be induced by this remedy—such, for instance, as a moderate blocking of the renal tubules,—and yet the case end fatally solely from the diphtheritic poison. When such cases have to be judicially investigated, great care and circumspection are necessary in forming an opinion upon them.[2]

There is among the various species of animals, and even among individual animals and human beings, a great difference in the susceptibility to the poisonous action of potassium chlorate. The reason for this, in the human subject especially, is by no means clear. Von Mering and

[1] v. Mering, op. cit., Versuch 108, S. 125.

[2] On this point see J. Hofmeier, 'Berl. klin. Wochenschr.,' 1880, S. 699.

others[1] have investigated the circumstances which accelerate or retard the changes in the blood resulting from the action of potassium chlorate. These changes are retarded by the addition of a small quantity of sodium carbonate. They are accelerated by larger quantities of the carbonate, by warmth, by carbonic acid and the acid phosphates, by diminished alkalinity of the blood, and by the presence of irregularly shaped red blood-corpuscles.

All these facts are of importance as regards the use of large doses of the remedy in the treatment of disease. It must be given cautiously when the temperature is high, and when the breathing or the circulation is embarrassed ; for in fever, as a rule, the alkalinity of the blood is lessened, and if there is dyspnœa the tension of the carbonic acid in the blood is raised, and thereby the alkalinity of the blood is also lessened. A large dose of the salt should not be taken on an empty stomach, as it will then be absorbed too rapidly. In disease of the kidney it should not be used, as, owing to the diminished secretion of urine, it may readily accumulate to an undesirable extent. When giving the remedy in large doses, it is well to avoid the simultaneous use both of free acids and of mineral waters rich in carbonic acid, or at all events, to limit the quantities.

In consequence of the discovery that dangerous symptoms sometimes follow the use of this drug, and of the discussions which arose thereon, an attempt was again made, but unsuccessfully, to exclude it from the list of officinal remedies. Considering its excellent effects in preventing, for instance, unpleasant stomatitis during a mercurial course, its exclusion would be a great loss to therapeutics. The dose, however, should be carefully regulated, and when the remedy is applied locally, the strength of the solution should not exceed 5 per cent. To a child of two or three years of age not more than 2 grammes (30 grains) should be given internally in the twenty-four hours, if less than twelve months old not more than 1·25 grammes (about 20 grains),

[1] Edlefsen, 'Verhandl. d. Congr. f. innere Med.,' 1884, S. 364; J. Cahn, 'Arch. f. exper. Path. u. Pharm.,' 1877, Bd. xxiv, S. 180; v. Limbeck, ibid., 1889, Bd. xxvi, S. 39; A. Falck, 'Arch. f. d. ges. Physiol.,' 1889, Bd. xlv, S. 304.

and to an adult not more than 6 to 8 grammes (90 to 120 grains) in the twenty-four hours. If these doses are not exceeded, and if they are given when the stomach is not empty,[1] poisonous effects will not be produced. When the patient refuses to take food, the use of the remedy should be limited to painting the mouth and fauces with a 5 per cent. solution.

We now come to a series of antiseptic and antizymotic preparations of an entirely different character; those, namely, which are classed among the organic compounds. Among these we will discuss first ACETUM PYROLIGNOSUM CRUDUM, crude pyroligneous acid, or wood vinegar.

This is a brown liquid having an empyreumatic odour, an acid and bitter taste, and depositing when kept a certain amount of tarry matter. It is produced, together with tar and certain gases, by the dry distillation of wood, and consists of water and from 4 to 10 per cent. of some of the lower fatty acids, chiefly acetic, together with methyl alcohol, $CH_3.OH$; acetone, $CH_3.CO.CH_3$; pyrocatechine, $C_6H_4(OH)_2$ and other incidental compounds, such as cœrulignone, $C_{16}H_{16}O_6$; furfurol, $C_5H_4O_2$; pyromucic acid, $C_5H_4O_3$, &c. Owing to the free acids and benzene derivatives which the crude wood vinegar contains, it may be usefully employed as a disinfectant for privies, drains, cesspools, &c.

ACETUM PYROLIGNOSUM PURIFICATUM, purified wood vinegar, is a clear, colourless or slightly yellow fluid, having a burning acid taste and smell, and is prepared by distillation from the crude preparation. By exposure to the air the colour becomes darker. The amount of acetic acid which it contains should not fall below 4·5 per cent. It naturally contains fewer tarry compounds and benzene derivatives than the crude vinegar, but its taste and smell clearly indicate that these products are still present in it.

[1] Seeligmüller, 'Deutsche med. Wochenschr.,' 1883, S. 657.

Experiments were made on animals with wood vinegar in 1820 by Justinus Kerner and others.[1] The results observed were a caustic action, and irritation of the nerves ending in paralysis, corresponding with those produced by the different constituents of the compound. Rectified vinegar also possesses marked antiseptic properties, and has been employed in the treatment of wounds and ulcers, and as a gargle or wash for the mouth, &c. It has also been administered internally in diseases accompanied by offensive odours, &c. As an external application the crude preparation is generally employed at the present day, and closely corresponds in its effects on anthrax spores with those produced by a 5 per cent. solution of carbolic acid.[2]

Creasotum, creasote, one of the substances contained in wood vinegar, is a colourless or slightly yellow oily liquid, which is only slightly darkened in colour, even on exposure to sunlight, and has a sp. gr. of 1·03 to 1·08. It is highly refractive, and has a penetrating smoky odour, and a strong burning taste. It is sparingly soluble in water, requiring 120 parts of hot water for solution; but is freely dissolved by alcohol, ether, and chloroform.

It was first isolated by K. Reichenbach from the tar of beech wood in 1832. As the odour, though of course much more powerful, strongly resembles that of smoked meat, he named it creasote (from κρέας, flesh, and σώζειν, to preserve), thereby indicating its strong antiseptic property. It is a mixture of certain ethereal derivatives of phenol, such as cresol, $C_6H_4.OH.CH_3$, in its two isomeric forms; phlorol, either in the form of dimethyl-phenol, $C_6H_3.OH.(CH_3)_2$, or of ethyl-phenol, $C_6H_4.OH.C_2H_5$; guaiacol or methyl-pyrocatechuic ether, $C_6H_4.OH.OCH_3$, which can also be obtained by the dry distillation of guaiac resin; and creasol—

$$C_6H_3.OH.OCH_3.CH_3.$$

The proportion in which these substances are present varies according to the temperature at which the distillation of the beech wood is conducted. When properly prepared, guaiacol and creasol are the chief ingredients.

[1] See Wibmer, op. cit., Bd. i, S. 12.

[2] R. Koch, op. cit., S. 249.

Creasote was employed therapeutically[1] very soon after its discovery. I can enumerate no fewer than sixteen monographs on its use, besides numerous articles in the medical papers, which were published previous to the year 1837. The effects produced by it were reported to be as follows :—Large doses rapidly caused death by paralysing the nervous centres. In moderate doses it generally induced symptoms of paralysis without spasm. It caused great irritation of the stomach and intestines, leading even to inflammation ; at first the mucous membranes appeared white, as if nitrate of silver had been applied to them. Bleeding vessels were stimulated to contract, and purulent discharges from mucous surfaces were checked, when it was applied in a properly diluted state.

Its antiseptic property, which is unquestionably very marked, was the one, however, which attracted most attention. Gangrene, cancerous ulceration, offensive wounds, and the like were the disorders in which it was especially employed, and this may have led to its internal use in ulceration of the lungs. Even in 1836 its use was recommended[2] in the treatment of consumption, and soon afterwards it was largely employed for that purpose. It soon passed out of fashion as a remedy, but within the last few years has again come into use. Bouchardat and Gimbert in 1877 again called attention to the neglected remedy, and from their numerous clinical observations, creasote seemed really to possess a specific action in cases of pulmonary consumption.

Fraentzel[3] was among the first to test the statements of the French authors. He was unable to corroborate their enthusiastic reports as to the certain and complete cure of the disease by creasote, but in his opinion the cough, expectoration, and fever were undoubtedly lessened by the remedy, and at the same time the purulent or offensive secretion from the bronchial mucous membrane was diminished

[1] K. Reichenbach, 'Das Kreosot in chem., physik., und medic. Beziehung,' Halle, 1833; 2 Aufl., Leipzig, 1835.

[2] J. Elliotson, 'Med.-chir. Rev.,' 1836, p. 463; Rampold, 'Hufeland's Journ. d. prakt. Heilk.,' 1836, Bd. lxxxii, Stück 5, S. 31.

[3] O. Fraentzel, 'Charité Annalen,' 1883, Bd. iv, S. 278; 'Therapeut. Monatshefte,' 1887, S. 193 u. 236.

and the general condition of the patient improved. The same results were produced also in acute phthisis. It seemed to him, therefore, beyond question that the progress of phthisical mischief in the lungs was materially checked by large doses of creasote.

Curschmann, who used creasote mainly in affections of the lungs accompanied by putrid expectoration, was also satisfied with the results produced by the remedy.[1] He directed it to be inhaled by means of an oro-nasal respirator, which he himself contrived, chiefly in cases which were accompanied from time to time with hæmoptysis. "In addition to its action as a styptic and powerful disinfectant, creasote," he says, "possesses the very great advantage, especially in cases of hæmoptysis, that it does not induce coughing; on the contrary, its action on most patients seems to be rather soothing than otherwise." R. Pick, of Coblenz, also observed practically the same results. Besides administering it internally, he specially directed that it should be inhaled, an apparatus of his own construction being used for the purpose. The direct effect, however, of this mode of treatment, in lessening the number of bacilli, remains open to doubt. Its action upon suppuration, and in preventing decomposition of the contents of the bronchi and cavities, is unquestionable.

With the rapid increase in the manufacture of gas for lighting purposes, a substance came into the market which was called creasote, but only somewhat resembled it, and by its greater cheapness supplanted the genuine preparation, costing, as it did, only one fifth of the price. It is obvious that the dry distillation of coal could not furnish precisely the same complex product as is obtained from beech wood. One main difference is that the former contains a considerable amount of carbolic acid, the latter little or none. But carbolic acid is not so well borne as those ethereal derivatives of it to which reference has already been made, and which constitute the genuine creasote. The absence of

[1] Curschmann, 'Berl. klin. Wochenschr.,' 1879, S. 429 u. 451; R. Pick, 'Deutsche med. Wochenschr.,' 1883, S. 189 und 204; Mosler und Holm, 'Therapeut. Monatsh.,' 1889, S. 211; J. Sommerbrodt, ibid., S. 298, and 'Berl. klin. Wochenschr.,' 1891, No. 7; Sahli, 'Corresp.-Blatt f. Schweizer Aerzte,' 1890.

convulsions in poisoning by the latter—which writers on the subject assert as a fact—is an indication of this. The irritation which induces a fit of coughing is allayed by inhalation of creasote, but aggravated by carbolic acid. R. Pick states that he has prescribed the former for months at a time, both for children and adults, without observing any drawback worth mentioning. Its use very rarely gave rise to any gastric disturbances, and never to the discoloration of the urine which occurs from the use of creasote only when it has been adulterated with carbolic acid, or when coal-tar creasote has been substituted for it.

The German Pharmacopœia has called special attention to the difference between these two preparations, and the tests which it gives for genuine creasote are of great practical value.

Creasote must be prescribed in fairly LARGE doses if it is to produce any appreciable results in a malady so deeply rooted as pulmonary comsumption. The German Pharmacopœia gives 0·2 gramme (3 minims) as the largest single dose, and 1 gramme (15 minims) as the largest dose to be given in a day. Experience has shown that the larger the quantity that can be tolerated, the better will be the result. The dose at first should be small, and should then be increased with caution, so as not to injure the digestion, and the remedy should be continued as long as possible. The best way to administer it is in the form of GELATINE CAPSULES, each containing 0·05 gramme (¾ of a minim). Creasote should never be taken on an empty stomach.

Moderate doses of creasote—0·05 gramme (¾ of a drop) three or four times daily—increase the peristaltic action of the stomach, as determined by the method previously described. When combined with alcohol this action appears to be increased to the extent of 120 per cent.

As we are aware, a substance was extracted from coal tar which chemists for a long time regarded as creasote, and this was named ACIDUM CARBOLICUM CRUDUM in the Pharmacopœia. Pure carbolic acid, ACIDUM CARBOLICUM, is obtained from the impure preparation by fractional distillation and subsequent purification. It consists of masses of long, slender, acicular crystals, which are colourless or have a faint reddish tinge,

and have a peculiar but not unpleasant odour. The acid is volatile and caustic. It melts at a temperature of from 40° to 42° C., forming a highly refractive fluid, which is soluble in 15 parts of water, and easily soluble in alcohol, ether, chloroform, glycerine, and solution of caustic soda. It can be obtained by dry distillation from many organic compounds, and is also found in small quantities in the excreta and urine of animals, especially of herbivora.

Runge, of Oranienburg, was the first who in 1834 obtained this product from coal tar, and he named it carbolic acid.[1]

Laurent and Gerhardt studied it more minutely, and the latter named it Phenol. The term Carbolic Acid is incorrect, as the preparation is not an acid. Runge himself states that it does not change the colour of litmus paper; nevertheless, on account of its readiness to unite with bases, he classes it among the acids. Phenol is an alcohol which is derived from benzol, C_6H_6, by the substitution of OH for one atom of hydrogen, forming $C_6H_5.OH$, in the same way as alcohol is derived from C_2H_6 by the substitution of OH for one atom of hydrogen, forming $C_2H_5.OH$. The compounds of phenol with the alkalies are decomposed by carbonic acid, but phenol does not displace carbonic acid from its compounds with the alkalies. Furthermore, from phenol we can obtain an ether, phenolic ether $(C_6H_5)_2O$, and various acid ethers, such as $C_6H_5.C_2H_3O_2$, as well as other compounds, indicating that it is an alcohol. Various hydroxyl derivatives of benzol and its compounds can be obtained, so that phenol has become a generic name, and the phenol now under consideration is termed Carbolic Acid.

The antiseptic properties of carbolic acid were recognised and known to its discoverer. He made a series of experiments with it, and considered that its action in this respect was due either to its coagulating, or combining with albumen. As tar, acetic acid, and creasote had previously been employed to deodorise offensive liquids, to purify the air from supposed miasmatic exhalations, and to prevent putrescence, it was natural that phenol, as a chemically uniform body, should gradually be employed in the same way. Its high price seems

[1] F. F. Runge, 'Ann. d. Phys. u. Chem.,' 1834, Bd. xxxi, S. 65, and Bd. xxxii, S. 308.

at first to have been a hindrance to its use, for it was not until Calvert, a manufacturing chemist in Manchester, prepared and sold the acid in large quantities, and published the results of his experiments, that physicians paid any attention to the compound. An exhaustive treatise upon it appeared in 1864,[1] and an able dissertation in 1866 by Buchheim;[2] and soon after J. Lister, then surgeon to the Glasgow Infirmary, founded, upon the results obtained by its use, his immortal doctrine of the antiseptic treatment of wounds.[3]

The action of carbolic is antiseptic and antizymotic, whether the decomposition be effected by organised or unorganised ferments. In the former considerable changes are observed to take place under the microscope when they are acted upon by carbolic acid. They become opaque, blackened, and granulated; any existing nucleus is clearly shown; and if sufficient carbolic acid has been added, the cells are rapidly disintegrated. It is evident that these changes are the result of direct paralysis, weakening, or destruction of the protoplasm. As a rule, organised ferments are far more sensitive than others to a protoplasmic poison.

Owing to the injurious effect carbolic acid exercises, even when greatly diluted, upon the vitality of cells, it will, when painted on the mesentery of a frog, check the formation of pus, which results from the active emigration of large numbers of the colourless blood-corpuscles. It penetrates the delicate wall of the vessel, and paralyses those organisms which adhere to its inner surface, as well as those about to pass through. The solution must be largely diluted, about 1 in 1600. No changes whatever are observed, either in the size of the vessels, the vascular wall, or in the rate of the blood-stream itself.

Paralysis of the cutaneous nerve-endings is probably also the cause of that ANÆSTHESIA of the skin which can be produced by the application, for a few minutes, of a concentrated

[1] J. Lemaire, 'L'acide phénique,' Paris, 1864, 2nd ed. 1865, 725 pp., small 8vo.

[2] W. Bucholtz, Dorpat, 1866.

[3] J. Lister, "On the Antiseptic Principle in the Practice of Surgery," 'Brit. Med. Journ.,' 1867, vol. ii, p. 246; 'Lancet,' 1867, vol. ii, pp. 353 and 668.

aqueous solution of carbolic acid, and may be usefully employed in slight surgical operations. If the solution is allowed to remain in contact with the skin for too long a time, the result may be complete destruction of the entire limb from dry gangrene, a danger which must be carefully borne in mind.

As early as the beginning of 1860 the POISONOUS ACTION of carbolic acid, not only on the lowest organisms, but also on the nerve-cells of the human subject, was carefully studied by Lemaire. To a child of eight years old he administered 0·5 gramme (about eight drops) in an enema. Only a small portion of this could possibly have been absorbed, yet "symptoms of stupor" supervened. He killed horses and dogs with it, and recognised that its caustic action produced convulsions, and paralysis of the brain and the medulla oblongata.

Unfortunately, we have abundant information as to its action upon the human subject. In the first place, I will describe to you, almost in the words of the medical man in charge of the case, the symptoms which were observed immediately after the poison had been taken.

A young man suffering from a rapier wound, which, however, was beginning to heal, took by mistake half a spoonful of carbolic acid, mixed with the same amount of glycerine, and was seen by the doctor immediately afterwards. He found the patient sitting up in bed, with his head bent, his face pale, and his mouth open, and the mucous membrane of the latter eroded. The mind was clear. Milk was at once administered, but symptoms of muscular weakness and twitchings, with those of commencing collapse, were already apparent. Attempts to induce vomiting by tickling the fauces with the finger did not produce the slightest effect. Tickling the throat with a feather then brought on temporary spasmodic closure of the mouth. Subsequent attempts to administer wine, in order to keep up the patient's strength, brought on spasmodic rigidity of the dorsal muscles. Presently he became completely unconscious and delirious; the breathing was laboured and stertorous, there was blueness of the face, and the temperature steadily declined. Violent convulsions, most strongly marked in the

lower limbs, now took place; there were considerable intermissions in the stertorous breathing, the pulse was scarcely perceptible, the face became blanched, and death then took place. During the later stages the pupils were widely dilated. There was no vomiting, nor were there any signs of severe internal pain. Death took place in from twelve to fifteen minutes after the carbolic acid had been taken. At the inquest it appeared that 8·5 grammes (about two teaspoonfuls) had been swallowed.

MISTAKES of a similar character—the administration of a strong solution of carbolic acid instead of the medicine which has been prescribed—have frequently occurred, and have been followed by equally sad results. I wish, therefore, most strongly to urge upon you how necessary it is that extreme caution should be exercised with regard to the administration of the remedies, when lotions of this character are prescribed simultaneously with remedies intended for internal use. If they are put into bottles of the same kind or size, neither labels, warnings, nor judicial decrees can prevent the occurrence of mistakes. The only absolutely safe plan is for the medical attendant himself to prepare, in the patient's room, the carbolic lotion of the necessary strength, in a wash-hand basin or wooden bowl; the patient is not likely to have a dose administered to him out of either of these vessels.

Experience has shown that the external use of carbolic acid may induce poisoning with unexpected rapidity in human beings, and this can also be easily demonstrated on warm-blooded animals. Very soon after the drug was discovered, my laboratory attendant applied a watery solution of it to the entire coat of a dog in order to destroy the countless fleas with which the animal was infested. About an hour later I found the dog lying unconscious on its side, foaming at the mouth, and trembling all over. In this condition it died. The same thing has been observed in the human subject.[1] Two young and otherwise healthy artisans rubbed themselves, nearly all over, with a solution of 30 grammes of carbolic acid in 240 grammes of water to get rid of scabies,

[1] A. Schmitz, "Zwei Fälle von Vergiftung mit Krämpfen nach Einathmen von Carbol," 'Centralbl. f. klin. Med.,' 1886, No. 15.

from which they were suffering. Each used 13 grammes (over 3 drachms) of carbolic acid. Even whilst applying it dizziness set in, with violent excitement and delirium, followed quickly, in the one case, by death from paralysis of the respiratory organs. The other recovered in the course of a few days.[1]

Peculiar effects, of various kinds, are produced from carbolic acid poisoning. One case[2] has been described of a patient who was suffering from pleurisy, and became rapidly unconscious after the injection of 3 grammes (45 grains) of carbolic acid into the pleural cavity. He was then seized with clonic spasms of the right arm, difficulty of breathing, and suddenly became totally blind. The pupils were widely dilated and absolutely insensitive to light, yet there was hardly anything abnormal in the condition of the fundus oculi. The blindness lasted longer than the unconsciousness. The mobility of the eye itself was unaffected. Clearly the poison had been freely absorbed into the system from the extensive pleural surface. The patient recovered.

The pupils are generally described as contracted; in the present instance the reverse was the case. We find a similar divergence in the reports with regard to the condition of the kidneys. In many cases there is no albumen present in the urine, while in others dissection reveals acute inflammation of both kidneys.

I will not enter into a detailed account of the effects of carbolic acid poisoning as observed in animals. The symptoms produced are, as in human beings, chiefly due to paralysis of the nerve-centres, with this difference, that there is also increased and involuntary muscular excitability, and that, consequently, general convulsive attacks are more common in animals than in man. On post-mortem examination nothing characteristic is observable, but simply the indications of local irritation, and such results as are due to paralysis of the brain and heart. There may be no apparent change observable in the blood resulting from the chemical action of the carbolic acid, although when they are directly mixed together the change is very marked, immediate disintegration of the blood-

[1] R. Köhler, 'Württemb. med. Corresp.-Blatt,' 1872, Bd. xlii, S. 41 und 49; Hoppe-Seyler, 'Arch. f. d. ges. Physiol.,' 1872, Bd. v, S. 470.

[2] A. Nieden, 'Berl. klin. Wochenschr.,' 1882, p. 748.

corpuscles being produced. The symptoms of poisoning may sometimes pass off, and then, after an interval of several hours, suddenly reappear in an acute form.

Very small doses of carbolic acid are completely oxidised in the system into carbonic acid and water; after large doses this is only partially the case, and almost half the amount may pass into the urine.[1] Carbolic acid does not appear to be eliminated by the lungs, and this is probably due to its combining with the alkali in the blood.

In former days it was observed that the urine became black or olive-green after inunctions with tar. The same change in the colour of the urine has frequently been noted after the external application of pure carbolic acid, and the cause has been carefully investigated. The urine contains compounds of carbolic acid and its derivatives,[2] and may be albuminous. The chief derivative is phenyl-sulphuric acid, $C_6H_5.HSO_4$,[3] also called from its constitution a sulphuric ether, together with small quantities of an alkaline phenyl-sulphate, the hydrogen being replaced by a monatomic base.

It has been proved by experiments on animals that these derivatives of carbolic acid are almost innocuous.

After large doses of carbolic acid, the amount of sulphates in the organism is insufficient for its entire conversion into phenyl-sulphuric acid, and it therefore appears in the urine, either unchanged, or as some other compound, such as glycuronic acid, owing to which the plane of polarisation is turned to the left, when the urine is examined by polarised light. The dark colour is due to the products of oxidation of the hydro-quinone and pyrocatechine—or more particularly of their ethereal sulphates—derived from the carbolic acid. If the discoloration is very marked, or if the urine is scanty and contains the slightest trace of albumen, the use of carbolic acid must at once be discontinued, and sodium sulphate must be given internally in order to form the inno-

[1] Tauber, 'Zeitschr. f. phys. Chemie,' 1879, Bd. ii, S. 366.

[2] A. Almen, ref. 'Zeitschr. f. analyt. Chemie,' 1871, Bd. x, S. 125; Baumann u. Herter, 'Zeitschr. f. phys. Chemie,' 1878, Bd. i, S. 247; A. Christiani, ibid., Bd. ii, S. 273; Baumann u. Preusse, ibid., Bd. iii, S. 156; E. Külz, 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxx, S. 474.

[3] E. Baumann, 'Arch. f. d. ges. Physiol.,' 1876, Bd. xiii, S. 285.

cuous phenyl-sulphuric acid or, more correctly speaking, its salt. Even before poisonous symptoms are developed, the sodium sulphate may be advantageously administered, to the extent of about 5 grammes daily in water.

In acute poisoning, when the carbolic acid has been swallowed, the stomach should at once be emptied and washed out, and the strength of the patient should be maintained by the means already described, and especially by the application of heat, as a rapid fall of temperature is one of the results of carbolic acid poisoning.

Experiments on animals have led to the recommendation of saccharated lime as an antidote.[1] This is prepared by adding five parts of quicklime to forty of water, and thoroughly mixing them with sixty parts of cane-sugar, then filtering and evaporating to dryness at a temperature not exceeding 100° C.[2] The compound of lime and carbolic acid is not very readily dissolved, and if well corked the compound of lime and sugar will keep for a considerable time, and is readily dissolved in water. Of course the antidote must be given as soon as possible after the poison has been taken, since carbolic acid is, as in the case above described, very rapidly absorbed by the stomach. The officinal Liquor Calcis, and the Calcii Carbonas Præcipitata, as well as a pulverised lump of chalk, may also be mentioned as antidotes. Though chalk is not the best remedy, it is one which can probably be obtained with the least delay.

A solution of 1 part of carbolic acid in 100 of water has been used for injection into the subcutaneous cellular tissue, as a local anodyne, and to subdue inflammation, and it is reported to have acted beneficially in inflammation of the joints and other affections. From five to six of these injections, each of 1 c.c. (fifteen drops), may be given in the twenty-four hours, without any poisonous effects being produced.[3]

It is a point of considerable interest, both practically and theoretically, that a solution of carbolic acid in oil is worth-

[1] Huseman, 'Deutsche Klinik,' 1871, S. 351.

[2] It seems to me preferable to precipitate the lime and sugar with alcohol, and then dry them in an atmosphere free from carbonic acid.

[3] Senator, 'Berl. klin. Wochenschr.,' 1876, S. 69.

less as a disinfectant.[1] The cause of this is that, owing to its greater solvent power, the oil does not liberate the carbolic acid in the moist tissues of the human body, nor in the aqueous media which contain the living germs or spores. For years, practitioners, in ignorance of this fact, have used these oily solutions of carbolic acid, and have certainly been often astonished to find that they were of little or no use.[2]

This is to pharmacologists a most instructive illustration of the way in which the efficacy of a remedy may be destroyed by some apparently unimportant substance.

When applying strong solutions of carbolic acid externally, two points should always be borne in mind; the possibility of poisoning being produced by the absorption of the acid through the unbroken skin, and the risk also of its causing mortification or mummification of the parts. The latter condition is very readily developed in the fingers and toes.

The Acidum Carbolicum Liquefactum of the Pharmacopœia is a mixture of 100 parts of carbolic acid with 10 of water; 33 parts of this mixture with 1 litre of water form Aqua Carbolisata. This "carbolic lotion," therefore, contains about 3 per cent. of chemically pure carbolic acid.

For some years the "Badische Anilinfabrik" has prepared carbolic acid synthetically. From the mild odour of this preparation, we may conclude that it is very pure, and free from the impurities which are derived from coal tar.

Carbolic acid is, we are told, hydroxyl-benzol. Now there are three isomeric dihydroxyl-benzols, $C_6H_4(OH)_2$, of which one, metadihydroxyl-benzol or Resorcin, is, in Germany, officinal. It consists of colourless or faintly-tinted crystals, with a peculiar, hardly perceptible, odour, and a sweetish rasping taste. Soluble in about an equal part of water, and in half the quantity of rectified spirit, or ether. It has a neutral reaction, and is completed volatilised by heat. It is prepared

[1] G. Wolffhügel und G. v. Knorre, in Struck's 'Mitteil a. d. Kaiserl. Gesundheitsamte,' 1881, Bd. i, S. 352, and R. Koch, ibid., S. 251.

[2] R. Koch, loc. cit., describes a case in which a patient died, who was inoculated with anthrax by a ligature which was made of sheep's gut, and had been preserved in carbolised oil.

from benzol, C_6H_6, and can also be obtained by heating galbanum, assafœtida, or ammoniacum with solution of caustic potash.

Resorcin has often been recommended for internal use instead of the ordinary antipyretics,[1] but the practice has not become general. Given in doses of 3 to 4 grammes (45 to 60 grains), it reduces the temperature in fever, but not, so we are told, without unpleasant collateral effects,—dizziness, stupor, and perspiration accompanying the decline, and rigors the rise of temperature. Quite recently it has been recommended again,[2] both in slight and severe disorders of the stomach and intestine, and also in nervous affections, such as the vomiting due to pregnancy or to peritonitis. No preparation is of service unless absolutely pure. The dose for adults, in the above-mentioned disorders, is from 0·1 to 0·5 gramme (1½ to 7½ grains).

Owing to its antiseptic and irritant properties, it is useful as an external application in skin diseases, in the form of solution, ointment, or paste.[3] Solutions of resorcin acquire a dark colour on exposure to light, and should therefore be dispensed in brown bottles.

On the other two dihydroxyl-benzols we may offer the following remarks.

Pyrocatechin, the ortho-compound, is a more powerful antiseptic than carbolic acid, and acts also as an antipyretic, But it has poisonous properties similar to those of the acid, and consequently possesses no advantages over it. The second, the para-compound, HYDROQUINONE, has attracted more attention. It possesses antiseptic properties, and is said to be a satisfactory antipyretic remedy, producing no special secondary effects.[4]

Hydroquinine corrects the reduced vascular tension asso-

[1] J. Andreer, 'Centralbl. f. d. med. Wiss.,' 1880, S. 497; 1881, S. 657, 769, und 913.

[2] H. Menche, 'Centralbl. f. klin. Med.,' 1891, S. 377.

[3] P. Unna, 'Ichthyol und Resorcin als Repräsentanten der Gruppe reducirender Heilmittel,' 1886.

[4] L. Brieger, 'Arch. f. Anat. und Physiol.,' 1879, Ergänzungsbd., S. 61; 'Centralbl. f. d. med. Wiss.,' 1880, S. 673; 'Zeitschr. f. klin. Med.,' 1881, Bd. iii, S. 25; A. Masing, 'Doctordissert.,' Dorpat, 1882.

ciated with the febrile state and restores it to the normal condition. This remedy also causes acute splenic tumours to contract.[1]

Hydroquinone and resorcin, as well as thymol, which we shall presently discuss, render the urine levo-rotatory, owing to the production of conjugated glycosuric acid.[2]

I will here interpolate, on account of its close relationship to hydroquinone, the description of an ancient remedy, the use of which has recently been revived. This is ARBUTIN, the chief constituent of bearberry leaves, Folia Uvæ-ursi, the leaves of *Arbutus* s. *Arctostaphylos uva-ursi,* belonging to the Nat. Ord. Ericaceæ, and growing wild in Germany and elsewhere. The leathery leaves bear a great resemblance to those of the whortleberry, *Vaccinium vitis-idæa,* but have a reticulated under surface, and are not dotted nor turned back at the edges.

Galen refers to the Pontic plant *ἄρκτου σταφυλή* as a remedy for hæmoptysis.[3] The bearberry leaves continued in use down to our own times, the effects they produce being attributed entirely to the large amount of tannic acid which they contain. This hypothesis, however, does not accord with the observed fact that tannic acid alone does not produce the same effects as an infusion of bearberry leaves. In 1852 Kawalier[4] prepared arbutin from them—a white crystalline substance, the formula for which is $C_{12}H_{16}O_7$. It has a bitter taste, and is soluble in water, rectified spirit and ether. In 1858 Jablonowski experimented upon himself with it.[5] He took about 18 grammes (4½ drachms) in forty-eight hours without feeling any particular effect from it. The urine passed subsequently was at first of a normal colour, but turned dark green after standing and dark brown when heated. The elder Schroff experimented with arbutin on healthy subjects, but did not observe any effect which could be attributed to it.

[1] O. Seiffert, 'Unters. über die Wirkungsweise von Hydrochinon,' u. s. w., Würzburg, 1883.

[2] E. Külz, 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxx, S. 484.

[3] Galenus, 'Opera omnia,' Kühn's edition, vol. xiii, p. 84.

[4] Kawalier, 'Ann. der Chemie u. Pharm.,' Bd. lxxii, S. 241.

[5] Jablonowski, 'Doctordissert.,' Dorpat, 1858, S. 28.

Arbutin together with H_2O is resolved into hydroquinone and sugar, by boiling with dilute acids, by various ferments, and by emulsine. The simplest formula for the process is—

$$C_{12}H_{16}O_7 + H_2O = C_6H_{12}O_6 + C_6H_4(OH)_2.$$

This chemical decomposition led to experiments being made with arbutin on animals.[1] It is transformed to some extent, in the bodies of rabbits, into sugar, methyl-hydroquinone and hydroquinone, both the latter being combined with sulphuric acid; a portion of it passes unchanged into the urine. In the human subject, doses of 5 to 9 grammes (75 to 135 grains) are said to have passed through the system almost entirely unchanged.[2] How far we are justified in assuming that, in the action of one or other of these substances, we have the explanation of what has been observed in patients suffering from bladder disease, is uncertain. Feibes found that a few decigrammes of arbutin added to 100 c.cm. of fresh urine, modified and retarded putrefaction. At all events, it may be admitted, as has in fact been clearly demonstrated in several instances,[3] that similar results may be produced in morbid conditions of the bladder, though it seems that arbutin is really beneficial, only when the cystitis is due to decomposition of the urine. A dose of 1 gramme (15 grains) three times a day proved effective, but there is no reason why more should not be given.

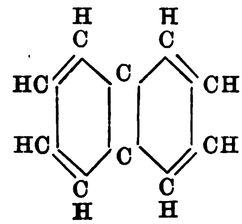
NAPHTHALIUM, naphthalene, $C_{10}H_8$, serves chiefly for disinfecting the alimentary canal. It consists of brilliant colourless crystalline plates, having a penetrating odour and a burning aromatic taste; it vaporises slowly at as low a temperature as 15° C, and melts at 80° C. It is insoluble in water, but readily soluble in rectified spirit, ether, chloroform, and liquid paraffin, and fairly so in fatty oils. Among other methods it is obtained by dry distillation from wood and coal. Chemically it is composed of two benzol-nuclei united (two

[1] L. Lewin, 'Arch. f. pathol. Anat.,' 1883, Bd. xcii, S. 517.

[2] E. Feibes, 'Doctordissert.,' Würzburg, 1884.

[3] H. Menche, 'Centralbl. f. klin. Med.,' 1883, S. 433; A. Schmitz, ibid., 1884, S. 777; Ungar 'Berl. klin. Wochenschr.,' 1884, S. 692; Paschkis, 'Wien. med. Presse,' 1884, No. 13.

carbon atoms being removed at the points of connection) in the manner represented in the accompanying diagram:



Naphthalene acts as a strong poison on the lowest organisms. In moderate doses it is readily tolerated by the higher animals and by human beings.[1] The fæces have no odour, or only that of naphthalene if it has been given in large doses, the greater part then passing through the intestines unchanged. The urine of patients who had taken naphthalene, in ordinary doses, remained unchanged for several weeks. In cases of chronic diarrhœa caused by intestinal cancer, &c., and accompanied with putrid odour, its use, even if it does not cure the diarrhœa, does away with the putrid odour. In some few cases the diarrhœa itself also ceases.

The following is a convenient form in which to administer the remedy:—℞ Naphthalini Puriss., Sacch. Albi, ana 0·25 (grana iv), Ol. Bergamott. 0·01 (♏︎$\frac{1}{6}$). M. f. pul. D. tal. d. No. 20. Sig. 5 to 20 powders, to be taken daily in wafers. For outward application, a solution in ten parts of oil is one way, among others, in which it may be employed. There is said to be one serious drawback to its use, namely, that when given for a considerable period it develops nephritis, methæmoglobin and hæmaturia; consequently, whenever the urine is observed to turn dark after standing, the naphthalene must be discontinued. Its use, moreover, has also produced strangury, scalding, and redness and swelling of the meatus urinarius. These symptoms all disappear when the naphthalene is discontinued, but the possibility of their occurrence makes

[1] E. Fischer, 'Das Naphthalin in der Heilkunde und in der Landwithschaft,' Strassburg, 1883; Rossbach, 'Verhandl. d. Congr. f. innere Med.,' Wiesbaden, 1884, S. 198; 'Berl. klin. Wochenschr.,' 1884, No. 46; E. Sherwald, "Naphthalin und Typhus," ibid., 1889, No. 19; L. Wolff, 'Med. News,' May 23rd, 1891.

it very necessary that caution should be exercised in the administration of the remedy. For children the dose to begin with is from 0·01 to 0·05 gramme ($\frac{1}{7}$ to $\frac{3}{4}$ of a grain). Many patients find the smell and the eructations resulting from naphthalene extremely nauseous. This unpleasantness can be avoided by giving it in pills, coated with keratin.

Naphthalene is said to be very effective in expelling *Oxyurus vermicularis* (Ungar). In order that as little as possible may be absorbed, and that it may pass on to the lower parts of the intestine, the patient should avoid fatty food while taking it.

By heating naphthalene for several hours with sulphuric acid, one atom of its hydrogen is replaced by hydroxyl, OH, and we obtain NAPHTHOLUM, naphthol, $C_{10}H_7.OH$, of which two isomers exist, dependent upon the position of the hydroxyl, α- and β-naphthol. The former is very poisonous, and is not used medicinally; the latter, on the contrary, is in Germany officinal. It is a white crystalline powder, and consists of brilliant colourless crystals, having a faint odour resembling that of carbolic acid, and a pungent, sharp, but evanescent taste. It melts at 122° C. It requires about 1000 parts of water for its solution, but is easily soluble in rectified spirit, ether, chloroform, and free alkali, and is also miscible with fats.

It is used externally, either in the form of lotion or ointment (about 1 in 100) in those skin diseases[1] for which tar was formerly employed. If used too freely, inflammation of the kidneys may ensue, with fatal results.[2] Naphthol is excreted in the urine, some of it unchanged and some of it in the form of an ethereal sulphate. A saturated solution of naphthol in hot water, when mixed with solution of perchloride of iron, should not develop a violet colour, as that indicates the presence of the poisonous α-naphthol.

The search for less poisonous antiseptics for surgical purposes led to THYMOLUM, thymol, being recognised as officinal. It consists of large, colourless, transparent crystals, with a thyme-like odour and an aromatic taste, a

[1] M. Kaposi, 'Wien. med. Wochenschr.,' 1881, Nos. 22—24; A. Neisser, 'Centralbl. f. med. Wiss.,' 1881, S. 545.

[2] M. Baatz, 'Centralbl. f. innere Med.,' 1894, p. 859.

neutral reaction, and melting at from 50° to 60° C. The crystals sink in water, but after being melted they remain liquid and float on the surface. They require 1100 parts of water for their solution, and are not soluble in glycerine; but they are freely soluble in spirits of wine, ether, or chloroform, and are readily volatilised in the vapour of hot water. The composition of thymol is $C_6H_3.CH_3.OH.C_3H_7$=methyl-isopropyl-phenol—that is to say, carbolic acid with methyl and propyl, each replacing one atom of hydrogen. It is a constituent of several ethereal vegetable oils, and more particularly of oil of common thyme.

Thymol[1] is strongly antiseptic, puts a stop to fermentation, deodorises offensive discharges from wounds, prevents suppuration, and promotes cicatrisation. Given in doses of 2·0 to 4·0 grammes (30 to 60 grains) it will even reduce the temperature in fever, though with less certainty than salicylic acid and quinine, of which we shall speak presently. Its action on the nervous system is the same as that of mild ethereal oils.[2] In the stomach it prevents the fermentative processes which arise from chronic catarrh, and from dilatation of that organ; in the intestine it paralyses the deadly parasite *Anychylostoma duodenale* more surely than any other anthelmintic. The quantity administered for this purpose during the day is from 4 to 6 grammes (60 to 90 grains). In the clinical wards at Bonn, Ungar found it very beneficial for infants, in attacks of diarrhœa accompanied with vomiting. The prescription used for the purpose was—Thymol 0·15 gramme (2¼ grains) rectified spirit 25 grammes (about 7 drachms), distilled water 75 grammes (about 21 drachms). One or two teaspoonfuls, according to the age of the child, to be taken several times a day. No unpleasant collateral effects were observed.

After the dose of thymol, above mentioned, had been

[1] L. Lewin, 'Centralbl. f. d. med. Wissensch.,' 1875, S. 324; 'Arch. f. path. Anat.,' 1875, Bd. lxv, S. 164; und 'Deutsche med. Wochenschr.,' 1878, S. 187; Husemann, 'Arch. f. exper. Path. u. Pharm.,' 1875, Bd. iv, S. 280; B. Kuessner, 'Habilitationschrift,' Halle, 1878; E. Bälz, 'Arch. d. Heilkunde,' 1876, Bd. xvii, S. 378; Bd. xviii, S. 344; H. Ranke, 'Samml. klin. Vorträge,' 1878, No. 128.

[2] See Vol. I, p. 356.

given to one patient suffering from anchylostoma, the urine when passed had a light brown colour, but on standing quickly assumed a deep reddish-brown colour, though it retained a strongly acid reaction. The same thing occurred in a patient who had taken thymol for an entirely different reason. In this case, the colour was proved to be due to an increased excretion of indican, induced by the large doses of thymol.[1]

The following preparation is not officinal, but its effects have been studied and referred to so constantly in the course of the last ten years, that it cannot be ignored here.

Oleum Eucalypti Globuli, eucalyptus oil, the ethereal oil extracted from the leaves of the *Eucalyptus globulus*, a tree belonging to the Nat. Ord. Myrtaceæ. It is a thin and almost colourless liquid. To prepare it for medicinal use, the oil must first be well shaken up with a weak solution of soda, to neutralise its acid reaction, and afterwards exposed to light and air for a considerable time. It is then ready for use. The colour is slightly yellow, the taste no longer pungent; and if taken into the mouth undiluted it causes first a sensation of warmth and then of cold, resembling the effect produced by oil of peppermint. Prepared in this way the oil is not poisonous, even when given to animals by the mouth in doses of 10 grammes (150 grains), or injected in corresponding quantities under the skin, but acts as an antiseptic and antipyretic. If allowed to evaporate freely on the mesentery of a frog, it immediately puts a stop to the emigration of the white corpuscles, that is to say to the formation of pus.[2] Externally, it is used chiefly in gauze dressings for the antiseptic treatment of wounds;[3] internally, a solution of 1 to 3 grammes to 180 of water (15 to 45 grains in 6 ounces of water)—a dessert-spoonful to be taken every two hours, or inhaled continuously—is employed in cases of bronchial catarrh with profuse expectoration, and for the

[1] K. Bohland, 'Deutsche med. Wochenschr.,' 1890, No. 48.

[2] C. Binz, 'Arch. f. path. Anat.,' 1878, vol. lxxiii, S. 187.

[3] Th. Siegen, "Das Eucalyptusöl zum antiseptischen Verband," 'Deutsche med. Wochenschr.,' 1880, S. 408, und 1881, S. 188; J. Lister, 'Lancet,' 1881, i, p. 837. For the earlier voluminous literature on the subject, see the monograph on its experimental and clinical use by Hugo Schulz, 'Das Eucalyptusöl,' Bonn, 1881.

paroxysmal attacks of coughing which are sometimes associated with phthisical mischief in the lungs.[1]

If a leaf of eucalyptus is held up to the light, numerous little oil-glands are seen scattered all over it. For a long time it was believed that the exhalations from these prevented the development of malarial fever, in the places where the tree grows. This theory, however, is untenable, for it is impossible to suppose that the oil, diluted so greatly as it must be in the atmosphere, could nullify the conditions which give rise to malaria. On the other hand, the eucalyptus, or blue gum tree, which in warm climates grows a metre in a year, and attains the immense height of 100 metres, may effect this by absorbing the moisture from the ground. For this reason it has been very largely planted in the malarial districts of Europe, and apparently with good results. A notable instance is the old abbey of Tre Fontane in the Roman Campagna, which is said to have become habitable by the Trappists in consequence of its introduction.

A valuable disinfectant for certain purposes, which sometimes fall within the province of the medical man is—

Carbo Ligni Pulveratus, Carbo Præparatus. This is the common charcoal of trade, freed from gases by being heated in closed vessels, and then powdered. When recently prepared, it is capable of absorbing the gases due to decomposition, such as ammonia and hydrogen sulphide; of the latter to the extent of fifty-five times its own volume. If unclean wounds are covered with it, or soiled articles of clothing laid in it, they lose their offensive odour. Stagnant water filtered through charcoal, becomes fit to drink, and water remains fresh for a long while, if kept in casks the inner surface of which has been carbonised. Human bodies enveloped in it immediately after death, do not become offensive, but decay in such a way that, after several months, hardly anything remains but bone and adipose matter, while the charcoal contains a quantity of nitric acid.[2] This result is said to be

[1] G. v. Schleinitz, 'Berl. klin. Wochenschr.,' 1882, No. 34; and Michaelis, 'Allgem. med. Cent.-Zeit.,' 1883, S. 81.

[2] J. Stenhouse, 'Charcoal for Sanitary Purposes,' 3rd edit., London, 1855.

due to the fact that finely powdered charcoal, freed from gas by heating, condenses the oxygen it absorbs, just as platinum-black does, and enables it to oxidise organic matter without forming the intermediate putrefactive products. The absorbent capacity of charcoal is not confined to the gases which arise from decomposition; for if solutions containing colouring matter or bitter extracts, alkaloids or metalloids—as, for example, phosphorus—or certain salts or metallic oxides, are shaken up with it and after a time passed through a filter, these various substances will be separated from the solutions and retained by the charcoal.

It is useless to administer powdered charcoal internally with the object of absorbing offensive gas, as the charcoal is rendered inoperative by the fluids, which it meets with. If its employment, in cases of sluggishness of the stomach and intestinal canal, associated with flatulent distension, have been followed by good results, these must probably be attributed to the local irritation of the mucous membrane, set up by the fine, sharp points of the powdered carbon. If introduced soon enough into the stomach after any substance has been taken, which can be absorbed by charcoal from watery solutions, it may prove useful by immediately combining with and retaining that substance.

The dose should be from 0·5 to 2 grammes (7½ to 30 grains). The use of powdered charcoal as an external application in surgical cases has been superseded by the new antiseptics. It is well adapted, however, on hygienic grounds, and when used in large quantities, for the disinfection of dead bodies, during transport from one place to another. To make it effective, it should previously be thoroughly calcined in a suitable vessel.

Carbo Animalis, animal charcoal, is prepared by exposing veal cut into small pieces, with about a third of its weight of bone, to a red heat, without the access of air. It consists of carbon, bone earth, and a trace of empyreumatic matter. It is less porous than wood charcoal, and the edges of its particles are much less acute and sharp, but it has a greater absorptive capacity for certain substances, owing to its being in a state of more minute subdivision, and also to the presence of calcium phosphates. If phos-

phorated oil is filtered through it, without the access of air, the filtrate no longer contains phosphorus. The use of animal charcoal has consequently been suggested as an antidote in poisoning from phosphorus, and for similar reasons as an antidote in poisoning from the vegetable alkaloids. At all events, if after any of these poisons have been taken, either kind of charcoal is administered, it will, at least, by enveloping the poison, impede its absorption by the walls of the intestines. Gases arising from putrefaction are less readily absorbed by animal charcoal, than by wood charcoal.[1]

[1] Eulenberg und Vohl, "Kohle als Disinfectionsmittel und Antidot," 'Vierteljahrschr. f. gerichtl. Med.,' 1870, Bd. xiii, S. 11.

XXIII.

Quinine—Obtained from cinchona bark—Historical details—Malarial fever—Experiments and the conclusions deduced therefrom—Amount of heat given off from the body—Effects of quinine on the oxidation of the tissues—Effects on healthy individuals—Post-mortem rise of temperature—Diminished excretion of nitrogen in the urine—Inhibitory action on the white corpuscles—Collateral effects of quinine—Poisonous effects—Preparations.

IT frequently happens, as has been already demonstrated with regard to carbolic acid and oil of eucalyptus, that those remedies which have an antiseptic action when applied externally have an ANTIPYRETIC [1] action when administered internally,—that is to say, they reduce the temperature of the body in fever, and moderate the attendant symptoms. In order to produce these effects it is, of course, essential that the remedy should exist in the organism for some time in a free state.

The scientific study of antipyretics is one which belongs essentially to our own times. It only became possible when, about the middle of the century, v. Bärensprung and Traube introduced at Berlin the use of the clinical thermometer, and since that time the study of antipyretics has also pharmacologically made most satisfactory progress. We will not stop in order to define the exact meaning of the word fever or pyrexia, but at once proceed to discuss the most important ingredient of cinchona bark, and the chief and most highly esteemed antipyretic remedy, namely, quinine.

CORTEX CHINÆ is the dried bark of the stem and branches

[1] From ἀντί and πύρ. A less correct expression is ANTIFEBRILE, ἀντί being there combined with a word derived from the Latin.

of cultivated plants of cinchona, more especially of the *Cinchona succiruba.* The bark is red when reduced to powder, and should contain at least 5 per cent. of quinine and other alkaloids. The native habitat of the cinchona is the mountain range of the Andes, from New Granada to Bolivia. *Kina,* the original name (or *Quina,* as it was written by the Spaniards, owing to the way they pronounced it) means in the language of the ancient Peruvians bark; *Kina-kina,* a good bark. From this the French have derived their present word *Quinquina,* the English their *Quinine,* and the Italians *China*—which, however, they pronounce as if spelt with a K. The Spaniards retain the word *Quina,* but pronounce it, also, as if spelt with a K. In Germany the Italian spelling has been adopted.

Linnæus gave the name of cinchona to this tree, in honour of the Countess del Chinchon (born in Old Castile in 1699), who was reported to have introduced the bark into Europe in 1640. It flourishes at an altitude of from two to eight thousand feet, and is conspicuous from its size and stately habit of growth. With a trunk no more than six inches in diameter, it may attain the height of from fifty to sixty feet.[1]

At the time of the introduction of cinchona bark the sanitary outlook in Europe was most unpromising. The injudicious arrangement and dirty condition of all kinds of dwellings, from palace to cottage; the constant pollution of the towns—hemmed in as they were by walls and moats—with organic refuse; the numerous swamps and fens of the country, which in the summer became dry and loaded with the decomposing remains of a luxuriant vegetation,—everything combined to ensure the development of fever, to promote its distribution and to give it a permanent resting-place. No remedy was known that was even fairly reliable, many and varied as were those recommended. Lingering illness and death from fever were as common as they were unavoidable. Such was the state of things when, in 1639, it was reported that in South America a new and almost infallible cure for fever had been discovered. Markham, the

[1] A. v. Humboldt, 'Ansichten der Natur,' 1849, Bd. ii, S. 318; 'Magazin der Gesellsch. naturforsch. Freunde,' Berlin, 1807, S. 60.

most distinguished investigator and the one best acquainted with the subject, tells the tale[1] somewhat as follows:

In 1638 the Countess of Chinchon, wife of the Viceroy of Peru, lay dangerously ill of a tertian fever at Lima, the capital. Don Francisco Lopez de Cañizares, the Corrigedor of Loxa, a town in the Andes, in what is now Ecuador, happened to hear of her illness. It is reported that, though the natives of Peru were not aware of the virtue of cinchona bark, the inhabitants of the more northern countries were familiar with it, and from them de Cañizares is said to have become acquainted with the febrifuge virtues of the bark. He sent a parcel of it to the Vice-queen, and the new remedy administered by her physician, Dr. Don Juan de Vega, effected a rapid and complete cure. The Countess returned to Spain in 1640, taking with her a large quantity of the precious bark, which she distributed in the unhealthy districts in the neighbourhood of her own home near Madrid. Her physician, Dr. de Vega, followed her, also bringing a large quantity of the bark to Spain, where he sold it at Seville for 100 reals the pound. It thus gradually became known in Europe, and was most appropriately called "Countess's powder" (*pulvis Comitissæ*). By this name it was long known to druggists and in commerce.[2] The Jesuits, too, the South American missionaries, did good service in introducing and extending the use of the bark.[3] The first publication on

[1] 'Peruvian Bark,' by Cl. R. Markham, C.B., F.R.S., pp. 9—11, London, 1880.

[2] The above statement now requires some modification, for according to a recent communication which I have received from Cl. R. Markham (the author of 'A Memoir of the Lady Ana do Osorio, Countess of Chinchon,' London, 1874) the following is the correct version of the part taken by the Chinchon family in the introduction of cinchona bark into Europe:—Ana do Osorio was the first wife of the Count of Chinchon, but she died before he went to Peru as Viceroy. His second wife was Francisca Henriquez de Ribera; and she was the lady who went out with him to Peru as Vice-queen, and was cured by the use of Chinchona bark. She left Peru in 1639, but died at Carthagena on the passage home. It was, therefore, the Count himself, not his Countess, who administered bark to the sufferers from ague on his estates in Spain.

[3] For a tolerably exhaustive *résumé* of the literature concerning cinchona bark and quinine down to 1867, see R. Wenz, 'Die thera-

the subject[1] appeared in 1642, and though the employment of the bark was strongly opposed at first as useless, dangerous, and harmful, yet by the end of the century it was generally recognised as an indispensable remedy. La Fontaine lauded its virtues in a poem of two cantos, the 'Poëme du Quinquina' for having cured Louis XIV of fever; and Madame de Genlis (1746—1831) wrote a charming novel relating to the manner of its discovery. Subsequently doubts were raised as to its efficacy, but, like opium, it passed through the ordeal with an undamaged reputation.

Since then cinchona bark has become more than ever indispensable, and its use has steadily increased. From a trade report it appears that nearly 224,000 kilogrammes (upwards of 220 tons) of quinine were manufactured in one year. The truth of this statement can only be realised, by taking into account the fact that quinine is efficacious, not only as a remedy, but also as a preventive against fever. In the exploration and settlement of distant lands, it is as indispensable as ammunition.

According to G. Schweinfurth,[2] it is no exaggeration to say that half of the travellers in Africa succumb to fever. It destroyed five out of the nine European members of the Tinne expedition in 1863. He himself kept in health, under the pernicious conditions of a prolonged stay in unwholesome lowland swamps, by taking about 0·5 gramme (7½ grains) of quinine daily as a precautionary measure, although he had to wade through marshes and papyrus beds in his botanical researches, and was more exposed than most travellers to malarial influences. He continued to do this without any injury to his health for quite two months, till in the purer air of the inland districts the dose was no longer necessary. And H. M. Stanley writes,[3] "These fevers reduced me seven

peutische Anwendung der Chinarinde und ihrer Alkaloiden,' Tübingen, 1867 (Doctordissertation). Further references will be found in C. Binz, 'Das Chinin nach den neuern pharmakologischen Arbeiten,' Berlin, 1875, and from that time up to 1894 in the subsequent notes to this chapter.

[1] P. Barba (Prof. d. Med. zu Valladolid), 'Vera Praxis ad Curationem Tertianæ,' Sevilla, 1642, 4.

[2] G. Schweinfurth, 'Im Herzen von Africa,' 1874, i, S. 137 und 352.

[3] H. M. Stanley, 'Through the Dark Continent,' London, 1878, i,

pounds in weight. But I quininized myself thoroughly from dawn of day to set of sun, and on the fifth day stepped out —sallow, pale, weak, and trembling, it is true, with jaundiced eyes, palpitating heart, and ringing ears,—but the fever had been conquered."

Nachtigal[1] calls quinine "the greatest boon for travellers in tropical regions;" and similar testimony comes from every tropical place where the workers with the ploughshare and the axe have to contend with the malarial poison, which emanates from the virgin soil.

In consequence of the large and increasing use of quinine, and the rapacious way in which the South Americans gathered the bark, serious danger arose that very soon no cinchona would be left. In the previous century the botanist La Condamine, who had carefully studied the cultivation of the cinchona tree, protested against the way the tree was being extirpated by the reckless manner in which the bark was gathered. Humboldt expressed his surprise to find that over 800 trees were cut down in order to obtain the 100 cwt. or so of the best bark, which was annually exported to the Spanish court from the district of Loxa in Bolivia. He observed, at the same time, that the older and thicker branches were becoming more and more scarce. So matters went on down to our own times. The inhabitants felled the trees without system and without restraint, careless whether they grew again or not, and from each tree only stripped so much of the bark as could be done without trouble. Then it was that the Government of Holland conceived the idea of acclimatising it in the warm highlands of their East Indian colonies. After many

p. 245. In a later place Stanley describes how he cured himself of malignant fever by taking 50 and 60 grains (3·3 and 4 grammes) at a time on two successive days, with a few drops of hydrobromic acid and an ounce of madeira:—"Like lightning the potent medicine courses through my veins. I feel its overpowering influence stealing rapidly over my fast bewildering senses." Then followed twenty-four hours of sleep, convalescence, and the slow recovery of the terribly enfeebled frame. ('The Congo, and the Founding of the Congo Free State,' 1885, i, pp. 273—275.)

[1] G. Nachtigal, 'Sahara und Sudan,' Berlin, 1879, vol. i, p. 734.

difficulties, Dr. Hasskarl of Cleves, whom they entrusted with the undertaking, succeeded, in 1854, in reaching Java with twenty-one cases of saplings, having already sent seed from Peru to Holland. The tropical heat had withered many of these saplings during the voyage, but the survivors grew so well, that at the present day the Government plantations contain millions of trees, supplying immense quantities of the bark. The Dutch Government has relinquished its monopoly, and willingly supplies cinchona seeds, and plants of the best varieties, to any person in the East Indies who is in a position to cultivate them. In 1859 the English followed their example. They sent out Mr. Cl. R. Markham,[1] who returned in 1860, bringing some hundreds of young plants with him. At the present date their plantations in Ceylon, in the Nilgiri Hills of Madras, and in the Sikkim Himalayas are in a most flourishing condition.

There are many distinct botanical varieties of cinchona, and a large number are cultivated, but the discussion of these varieties need not detain us. The constituents of the cinchona bark which are medicinally of importance are the alkaloids, the bitter extract quinovin, and tannic acid. We will now discuss the most important of these, namely :—

QUININE.—This was discovered in 1820 by Pelletier and Caventou. Liebig and Regnault determined its composition and Strecker its formula, which, in an anhydrous state, is $C_{20}H_{24}N_2O_2$. In this condition it appears as an amorphous amber-like substance. The hydrate CHININUM, is white, crystalline, and bitter to the taste, soluble in 1680 parts of water, and very readily soluble in rectified spirits, in 60 parts of ether, 2 parts of chloroform, and 200 of glycerine. It is a diatomic base, replacing ammonia, neutralising acids completely, and forming a series of salts. Its empirical formula is most nearly related to that of strychnine, $C_{21}H_{22}N_2O_2$, from which it differs in containing one atom less of carbon, and two atoms more of hydrogen.

In accordance with the customary method I should, in describing the ACTION of quinine, begin with an account of its action on the blood-pressure, the vaso-motor system, the

[1] Cl. R. Markham, 'Travels in Peru and India,' London, 1862; 'Parliamentary Blue-books,' London, 1863, No. 118; 1866, No. 353.

respiratory centre, the brain, spinal cord, &c. All these details have been carefully studied, but have furnished no explanation of the way in which quinine acts therapeutically;[1] all that has been gained is some slight insight as to the reason why it sometimes acts injuriously. I therefore proceed to discuss the facts which clinical observation has firmly established with regard to the action of quinine upon the human frame. The following are the conclusions which have been reached:

1. Given on a day when the patient is free from fever, it LESSENS OR PUTS A STOP TO an expected paroxysm of malarial poisoning.

2. In chronic cases, it cures or ameliorates the cachexia resulting from malaria.

3. It acts as a PREVENTIVE in many cases against infection by malarial poisoning.

4. It lowers the temperature in many continuous fevers,—enteric fever, for example.

5. In healthy subjects it moderates the daily rise of temperature.

These results follow upon doses of 0·5 gramme (7½ grains) and upwards. Smaller doses only take effect if frequently repeated until the above amount is taken. Otherwise they only act as a simple bitter.

The first three points are, so far as we are at present concerned, the most important, for malarial or intermittent fever, or ague, is a disease which is peculiarly under the control of quinine. The effect of the remedy is so certain and lasting as to surpass all other pharmaco-therapeutic actions with which we are acquainted. How shall we best describe them?

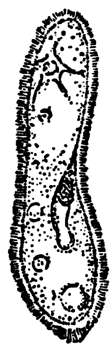
Though quinine is readily tolerated even in large doses by the nerve-cells in the human subject, neutral or slightly basic solutions of it nevertheless act energetically as poisons on many kinds of protoplasm, and more especially on that of the lowest organisms.

If to a drop of a vegetable infusion containing the larger and easily observed infusoria, placed under the microscope,

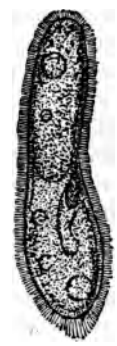
[1] For further particulars see my article "Chinarinde," in Eulenberg's 'Real-Encyklopädie,' Wien und Leipzig, 3 Auflage, 1894.

we add a drop of a solution of quinine, the strength of which is about 1 in 200, we notice that the organisms which were previously swimming actively about are immediately paralysed. They lie motionless, almost at once appear as dark granules, and quickly become disintegrated.

If the solution is more dilute, the paralysis of the organisms is produced at a correspondingly slower rate, and is less intense and destructive. But even when the solution of quinine was so dilute as 1 in 10,000 (that is to say 1 in 20,000 when added to a drop of the infusion), vigorous Paramecia, in an infusion of hay, showed, within five minutes, signs of incipient paralysis, and in two hours were motionless. A few hours later they were completely disintegrated. Here, exhibited under two microscopes, is a repetition of the particular experiment which I described in 1867.[1]



Healthy Paramecium from the upper layer of an infusion of hay, magnified 600 times.



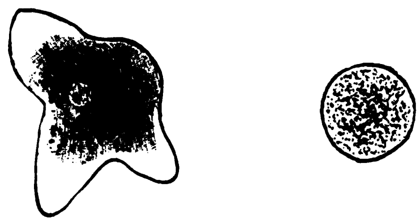
Paramecium from the same liquid after six hours' exposure to a neutral solution of hydrochlorate of quinine, 1 in 50,000. Movement distinctly retarded.

This simple experiment is a ready illustration and explanation of what I have stated. The same effect which you see produced here on a large and active Paramecium is also produced on all the other minute organisms, which subsist on decaying vegetable matter and are to be found in fresh water, at least so far as I have been able to investigate the matter.[2]

[1] C. Binz, 'Centralb. f. d. med. Wissensch.,' Berlin, 1867, p. 308.

[2] C. Binz, 'Wirkung antiseptischer Stoffe auf Infusorien von

This is especially the case with the amœbæ of fresh water.[1] Under the microscope we see one of these, as represented by the figure on the left, in active movement



Pflanzenjauche.' Others are even more susceptible. W. Krukenberg, in his 'Vergleichend-physiol. Studien an den Küsten der Adria,' 1880, i, S. 8, says:—"I was able to make certain, by very varied and oft-repeated experiments, that the Turbellaria (Polycelis) are no less sensitive to the action of quinine than the Infusoria, while worms, Medusæ, and Actiniæ resist it. In every case I found that the Polycelis died in a neutral hydrochlorate solution of quinine—1 in 10,000—in from thirty to forty minutes, and became opaque from coagulation of the parenchymatous tissue; in a solution of only 1 in 100,000 the Turbellaria died in a few hours, although they remained quite lively, for days, in an equal amount (about 20 grains) of water."

In a subsequent letter to me this investigator says:—"A neutral solution of quinine destroys Turbellaria in a few hours. Of all other vegetable bases, the action of which I have tested upon them, as strychnine, veratrine and curarine in the form of curare, only veratrine seems to approximate to quinine in its effect. Although I used much stronger solutions, such as 10 and 25 per cent., of the other alkaloids, the Polycelis lived longer in them than in the 1 in 1000 solution of quinine. Yet I know of hardly a single fact which would lead us to conclude that the species of Turbellaria in question are affected in an unusual degree by variations in the strength of the solutions, or by cold, &c. This I observed particularly in an unpublished experiment in which I increased the amount of common salt in fresh water up to 3 per cent."

Ch. Darwin, in his 'Insectivorous Plants,' London, 1875, pp. 201, 202, referring to my experiments respecting the properties of quinine as a poison for many forms of protoplasm, gives an instance from which it appears that a solution of 1 in 1000 of quinine sulphate, with basic reaction, rapidly destroys the tentacles of the *Drosera rotundifolia,* and gives them an appearance similar to that produced by "very hot water."

[1] C. Binz, "Die Einwirkung des Chinins auf Protoplasm bewegungen," 'Arch. f. d. mikroscop. Anat.,' 1867, Bd. iii, S. 383.

pushing out its hyaline substance in every direction, and constantly changing its form; the transparent margin, however, is clearly distinguishable from the inner part, which is slightly granular, and contains the nucleus. The figure on the right represents another amœba, from the same drop of water, after being exposed for six hours to a solution of 1 in 50,000 of neutral hydrochlorate of quinine. It presents a spherical form,—that is to say, it is in a state of tetanic contraction; its substance is coarsely granular, and it has ceased to move: if not dead, it is at any rate profoundly affected. If the strength of the solution of quinine were raised to 1 in 1000, instant death and rapid disintegration of the tissue would take place.

This action upon the lowest forms of organic life is peculiar to quinine. Other neutral bitter extracts possess hardly any trace of it, and very little effect is produced by the other officinal vegetable alkaloids, excepting those which, like strychnine and veratrine, are extremely poisonous to man. On the other hand, I have met with very low organisms which continue to live in a solution of 1 in 500 of quinine as if it were their native element.[1] Among these are the amœbæ found in salt water, the Euglena, which develop the green covering frequently seen on the waste-pipes on the sunny side of a house; and also the spirilla of relapsing fever.[2] The spirilla of ordinary vegetable decomposition are acted upon by quinine so readily that a solution of 1 in 10,000 renders them motionless, while those of recurrent fever may be bathed in it, without any visible effect being produced upon them.

At a time when the view was generally entertained by the medical profession that quinine cured malarial fever by its action upon the nervous system, I drew from these and allied experiments the following conclusion:[3]

"It is incontestable, in the present state of our knowledge, that malarial disorders, many forms of typhus, pyæmia following surgical operations, and—as the experi-

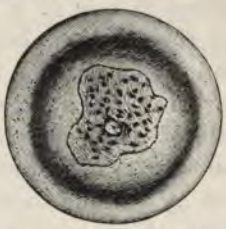
[1] O. Conzen, 'Experim. Untersuchungen über einige Ersatzmittel des Chinins,' Doctordissert., Bonn, 1868, S. 28.

[2] Engel, "Ueber die Obermeier'schen Recurrensspirillen," 'Berl. klin. Wochenschr.,' 1873, p. 411.

[3] C. Binz, 'Experimentelle Untersuchungen über das Wesen der Chiniwirkung,' Berlin, 1868, S. 26.

ments devised by Semmelweiss clearly prove—puerperal fever, are fermentative changes resulting from the absorption of septic matters into the blood. These septic substances vary in character, as do also their effects upon tissue metabolism; but they agree in their most important effect, namely, the development of an abnormal or morbid metabolism of the tissues, which is accompanied with high temperature and rapid disintegration. The ferment of some of these septic matters REPRODUCES ITSELF, and is easily communicable, but it is doubtful whether they all possess these powers; whether THIS FERMENT is *one of the lowest organisms*, similar to those causing zymotic and putrefactive changes, is a question which still awaits final decision."

Further investigation has shown that my views on the subject, though much controverted both at the time and since, were correct; we have now become acquainted with the amœboid parasite or parasites, which produce malarial fever by effecting a lodgment in the red blood-corpuscles,



Red blood-corpuscle containing fully developed malarial amœba.

and we know from numerous authorities that after the administration of quinine and its absorption into the system these parasites immediately disappear from the blood of the patient. A. Laveran's[1] discovery of the amœba of malaria

[1] In his book, 'Traités des fièvres palustres avec la description des microbes du paludisme,' 1884, p. 491, and again in his 'Paludisme et son hématozoaire,' 1891, pp. 3 and 183, Laveran discussed my researches on the subject of quinine, though he was evidently acquainted with them only through misleading summaries and incorrect quotations, which have long since been refuted by myself and others. For a proof of this see 'Berl. med. Wochenschr.,' 1891, No. 43. On the destruction of pathogenetic amœbæ by quinine see F. Lösch, "Massenhafte Entwickelung von Amöben im Dickdarm," 'Arch. f. pathol. Anat.,' 1875, Bd. lxv, S. 196; from E. Eichwald's clinic at St. Petersburg.

has been confirmed by numerous investigators; and the only natural explanation of its disappearance from the blood under the action of quinine is that this substance, acting as a poison on protoplasm, directly attacks the amœba and arrests its further development. The result of all investigations, without exception, has been to prove that within a few hours after the absorption of quinine into the blood of a patient suffering from malarial fever, the parasites are found to be in a disorganised condition, verging rapidly upon disintegration; they have lost their specific property of absorbing certain colouring matters, and their spores, though these may still be formed, have lost the capacity of developing into fresh amœbæ. In short, we see the poisonous action of quinine on the protoplasm manifested in the most varied ways, developing in it, at first, increased movement, which rapidly ceases and is followed by complete paralysis and disintegration. That the spores of the malaria amœba should not disappear so quickly after the administration of quinine as the amœbæ themselves do is in accordance with clinical experience, and with the view above mentioned. The spores are capable of great resistance to the action of quinine, and the remedy is only efficacious when given long enough before the attack to prevent their development into fresh amœbæ.[1]

This finally disposes of the far-fetched theories (most of them based on the supposition that the nervous system[2] took some part in the process) which were formerly offered in explanation of the cure of malarial disorders by quinine; all these theories were declared by Griesinger in 1864 to be inapplicable.[3]

[1] For details I refer the reader to the monograph by J. Mannaberg, 'Die Malariaparasiten auf Grund fremder und eigener Beobachtung dargestellt,' Wien, bei A. Holder, 1893, with four coloured plates. Here also, in 246 parts, may be found the entire bibliography of the subject.

[2] P. Briquet, 'Traité thérapeutique de Quinquina,' Paris, 2nd ed., 1855. On p. 342 of this work, in the chapter on "Maladies intermittentes," it is stated that "la spécialité de l'action du quinquina étant bien determinée, la raison indique que son influence ne peut s'exercer *que sur le système nerveux.* Il ne reste plus qu'à rechercher de quelle manière se produit cette influence," &c.

[3] Griesinger, 'Infectionskrankheiten,' 2 Aufl., 1864, S. 67.

The fact that malarial disorders can be PREVENTED by the use of quinine, also points to a direct relationship between the virus and the remedy. This prophylactic power has been denied. But the reason for doing so was based on the results of experiments which were not conducted in a satisfactory manner. Anyone who has been accustomed to experimental investigation is aware that positive results cannot be expected from small irregular doses, nor even from large single doses taken at long intervals, but only from the continuous administration of moderate quantities. That this mode of treatment is effective is proved by the published reports of trustworthy observers. Its successful application was illustrated in a striking manner not long ago.[1] No worse fever den exists in the civilised world than the harbour of Tandjong-Priok, in Java. Hardly a single sailor who arrives there escapes severe attacks, but it was found that the frequency and severity of these attacks could be immensely reduced by daily doses of 1 gramme (15 grains) of quinine in a little brandy, taken for three or four days before reaching the harbour, while those persons who omitted this precaution suffered as usual from the disease.

There are cells of another kind which have shown themselves to be particularly susceptible to the action of quinine, namely, the lymph corpuscles or colourless blood-cells, which live and are distributed within our own organism in immense numbers. If quinine is added to the blood in as small a proportion as 1 in 20,000,[2] their amœboid move-

[1] C. Graeser, 'Berl. klin. Wochenschr.,' 1888, Nos. 42 und 53; Hertz, in v. Ziemssen's 'Handb. d. speciellen Pathol. und Therapie,' 1877, Bd. ii, S. 869. This also contains references to other publications on the subject. For fuller details see v. Vivenot, 'Wiener med. Jahrbücher,' 1869, Bd. xviii, S. 39. Arsenic also has a prophylactic virtue according to Tommaso-Crudeli, "Sulla Preservatione dell' Uomo nei paesi di Malaria," 'Transactions of the Acad. dei Lincei,' Rome, 1880, 5, 22; and 1883, 7, 134.

[2] This figure is quoted from one of the best authorities on protoplasm, Th. W. Engelmann, of Utrecht, cf. the 'Arch. f. Anat. u. Physiol.' (Physiol. Abtlg.), 1885, S. 148. It goes beyond my own published opinions on this subject from the year 1867 ('Arch. f. mik. Anat.,' Bd. iii, S. 383). In a letter addressed to me and reproduced in the 'Archiv' above referred to, Engelmann has withdrawn his strictures, published in L. Hermann's 'Handbuch der Physiologie,' upon my

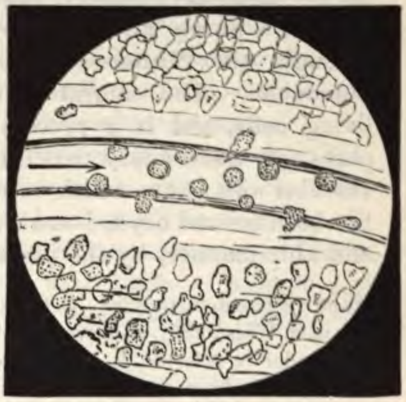
ments are noticeably checked, and if a larger quantity is added they become, almost instantaneously, coarsely granular and perish. Even the application of heat fails to develop in them the slightest movement. They remain globular, their nuclei are distinct and swollen, and the cells themselves have lost their adhesiveness.

Further, if the mesentery of a healthy frog is laid bare, and a full dose of hydrochlorate of quinine is at once injected and the injection repeated at intervals—the doses, however, not being so large as to stop the action of the heart—no pus will be formed; whereas if a control frog be placed beside it, with its mesentery exposed, the latter will, in a few hours, be entirely covered with pus. If, however, the injections of quinine are administered after suppuration has taken place (see Fig. A), we perceive that the number of white corpuscles which then

FIG. A.

Normal suppuration.

FIG. B.



Suppuration modified by the action of quinine.

migrate through the vascular wall (Cohnheim) becomes steadily fewer.[1] Those which have already migrated pass

assertions with respect to quinine and the white corpuscles. See also the 'Arch. f. path. Anat.,' 1891, Bd. cxxv, S. 196. A translation of Engelmann's letter will be found in the 'Quarterly Journal of Microscopical Science,' London, Oct., 1884, New Series, Nr. 96, p. 682.

[1] Figs. A and B represent the same capillary vessel before and after the subcutaneous injection of quinine. The arrow simply indicates the course

in the mesentery further and further from the vascular wall, and are not followed by others, or at most by only a few; and thus, WHILE THE CIRCULATION GOES ON UNDISTURBED AT A RATE FAVOURABLE FOR THE FORMATION OF PUS, a clear space (see Fig. B) is seen running parallel to the vessel under observation, which demonstrates as distinctly as the previous experiment did, the effect of quinine in restraining suppuration. Meanwhile fewer colourless corpuscles are seen in the blood-vessel itself, and those which are seen have somewhat the same appearance as was presented by the corpuscles in a previous experiment when quinine was added to a drop of blood. The paralysis of the white corpuscles is, of course, less complete in the present experiment, since the quinine is more largely diluted. Even when the quinine is producing its full effect some of these corpuscles retain strength enough to penetrate the vascular wall.

The conclusion which Cohnheim arrived at with regard to his discovery, namely, that the migration of the leucocytes is a purely physical act—a filtration of the leucocytes through the "altered" vascular wall,—seems to me untenable.[1] The migration is essentially an act of the living cells, and is a process in which the blood-pressure plays only a secondary part; the "altered condition" of the vascular wall is one which results from the migration. This has been proved beyond doubt, and in a singularly conclusive and able manner, by the investigations of Lavdowsky.[2]

of the red blood-corpuscles. C. Scharrenbroich and C. Binz, 'Centralbl. f. d. med. Wiss.,' 1867, S. 817. For confirmation of the above statements, the reader is referred to the following amongst other authorities:—G. Kerner, 'Arch. f. d. ges. Physiol.,' Bd. iii, S. 93, mit der Tafel II; Bd. v, S. 27; Bd. vii, S. 122; Appert and Arnold, 'Arch. f. path. Anat.,' 1877, Bd. lxxi, S. 364; Pekelharing, ibid., 1886, Bd. civ, S. 242. Cf. also Binz, 'Arch. f. exper. Path. u. Pharm.,' 1877, Bd. vii, S. 282; Scharrenbroich, ibid., 1879, Bd. xii, S. 33; and Binz, 'Centralbl. f. klin. Med.,' 1887, S. 545. Kobert u. L. Schumacher, 'Arbeiten d. pharmakol. Inst. Dorpat,' 1895, Bd. x, S. 1—65 (the most exhaustive paper on the subject).

[1] C. Binz, 'Arch. f. path. Anat.,' Bd. lix, S. 293; Bd. lxxiii, S. 181; Bd. lxxxix, S. 389.

[2] M. Lavdowsky, "Mikroscopische Untersuchungen einiger Lebensvorgänge des Blutes," ibid., 1884, Bd. xcvii, S. 177.

Considerable importance is now assigned to these corpuscles, since investigations made within the last fifteen years have shown that those organs of the body, the structure of which is composed largely or entirely of these corpuscles, are the parts in which the spores or germs of infectious disease are developed, and thence distributed throughout the system. I mean such organs, for instance, as the spleen, and the glands of the small intestine. Moreover in all acute diseases which are accompanied with exudation of some sort, such as pneumonia and purulent peritonitis, the number of colourless blood-corpuscles is increased in a remarkable degree; whereas in those infectious diseases which are unattended with any considerable exudation into the tissues, such as enteric and malarial fevers and septicæmia, this "inflammatory leucocytosis" does not take place, and, even when the temperature is highest, no increase can ever be discovered in the number of leucocytes. Even Briquet refers to the efficacy of quinine in checking commencing suppuration. And every physician knows of instances in which a few large doses of quinine have favourably influenced the course of disease, reduced the fever, maintained the strength, and arrested the inflammatory changes.

Metschnikoff's theory of phagocytosis does not contradict my view, because, in the first place, in spite of its wide bearing, phagocytosis does not hold good as regards all micro-organisms, and as applied to inflammatory leucocytosis the theory is unproved, and even improbable. Mannaberg, speaking from experiments and observations made by himself and others, says:

"In spontaneous recovery from malarial fever the colourless corpuscles of the blood do actually appear to play the part of phagocytes; in the cure of it by quinine this action is not necessary nor admissible, as quinine has the same effect upon the phagocytes as upon the amœbæ of malaria. The investigations of Golgi, among others, prove this. He noticed a decline or impairment of the phagocytic process in the blood, as a direct consequence of the administration of quinine."

Again, it has been asserted that quinine lessens the daily normal rise of TEMPERATURE, in healthy subjects, and reduces

still more decidedly the febrile temperature, in many acute diseases. How are these two results produced ?

Of the two possible hypotheses, one may immediately be discarded, namely, that which attributes the decline of temperature to an increased loss of heat from the body. This view has been advanced, and was based upon some extremely faulty experiments ; but it has been disproved by some other experiments, both on animals [1] and on man,[2] which agree in their results.

Although, after the administration of nitrite of amyl, or alcohol, to a healthy man, the temperature immediately rises, as is shown by placing a thermometer upon the skin and carefully covering it over, when quinine is given, even to the extent of 1·25 grammes (about 20 grains) at a time, the temperature does not vary in the slightest degree; and in animals, much larger doses—in proportion to the weight of their bodies—likewise fail to produce any change. The action of quinine has also been proved to be independent of the loss of heat from the body, by gasometric experiments upon animals in a febrile condition. Fever was induced by injections of putrid matter, and the animal's temperature was then taken, and its CONSUMPTION OF OXYGEN noted. While the former sank in the usual fashion two or three degrees after giving quinine, the average consumption of oxygen, reckoned in c.cm., without and with quinine, by an animal weighing 1 kilo., was in one hour as follows :

WITHOUT QUININE.	WITH QUININE.
4 experiments = 600·8	4 experiments = 511·5
4 " = 673·6	2 " = 402·2
	5 " = 443·6

To render any loss of heat by radiation impossible, the animals were put into a bath, the warmth of which closely

[1] H. Arntz, "Ueber den Einfluss des Chinins auf Wärmeabgabe und Wärmeproduction," 'Arch. f. d. ges. Physiol.,' 1883, Bd. xxxi, S. 531. A second report in the 'Centralbl. f. klin. Med.,' 1885, S. 553. The investigations were conducted partly under Finkler's and partly under my own direction.

[2] Fr. Müller, "Die Korperwärme im heissen Dampfbad unter dem Einfluss fieberwidrige Substanzen," from C. Gerhardt's 'Mitteil. d. med. Klinik zu Würzburg,' 1886, ii, S. 149; R. Gottlieb, 'Arch. f. exper. Path. u. Pharm.,' 1891, Bd. xxviii, S. 167.

corresponded with that of their mean temperature, or was sometimes a trifle lower and sometimes a trifle higher. The experiments were so arranged that the respiration and circulation were unaffected. The results admit of only one conclusion,—that THE ABSORPTION OF OXYGEN BY THE TISSUES, which is the chief factor in maintaining the bodily temperature, is diminished by quinine.

In the wards for syphilis and skin diseases at Würzburg, the temperature of some of the patients, who were subjected for fifteen minutes to a vapour-bath at 45° to 46·5° C. (113° to 115·7° F.), was determined by one or more experiments. The temperature was taken in the rectum. Two grammes (30 grains) of quinine were then given to the patient, six hours before taking the vapour-bath, and the result proved that under the influence of quinine the temperature DID NOT RISE SO HIGH as in the experiments made without it. The total number of experiments made on four persons was seventeen without, and seven with quinine. Now, as an external temperature of 45° C. (113° F.) precludes the possibility of loss of heat, by radiation, from the human body, the temperature of which is lower by about 8° C. (14·4° F.), it is equally impossible that the lower register of the thermometer, when the patient was under the influence of quinine, could be caused by increased radiation of heat. The only conclusion left is that there is a reduction in the amount of heat generated; and this, as we have many reasons for knowing, may, in the case of fever patients, be effected either by paralysing the cause which gives rise to the fever, or by lowering the morbid activity in the cells, either directly or through the agency of the nerve-centres which control them.

It is certain that the brain and medulla oblongata take no essential part in lessening the generation of heat. Some time ago I was able to prove, as I had already done in the case of alcohol, the antipyretic action of quinine upon large animals after section, under ether, of the spinal cord, thereby eliminating the action of the chief nervous centres. The loss of heat externally, from the animals, was obviated by placing them in a room the temperature of which was maintained at from 28° to 30° C., and by wrapping them in

thick wadding.[1] I need not here discuss the question why, by these means, any action of the sympathetic nervous system was in all probability excluded. In three of these experiments, after the administration of quinine I observed the post-mortem rise of temperature. According to the generally accepted view, this results from the temporary continuance of chemical changes within the body, whilst the loss of heat from the skin is considerably diminished. This post-mortem rise is particularly marked (1° to 2° C.) when the animals die in the warm chamber. In two of these experiments the rise was very slight ($0{\cdot}3^\circ$ and $0{\cdot}4^\circ$ C.), and in one, where there was a delay in taking the temperature, after the remarkably short period of ten minutes, no increase could be detected. The conditions were extremely favourable both for the development of heat and for its continuance.

This post-mortem result, which was absolutely independent of any action of the brain or circulation, clearly indicates that one effect of quinine is simply to inhibit the chemical changes in the organism. This view is confirmed by the diminished putrefactive changes which occurred in the dead bodies of the animals; for, as is well known, decomposition invariably takes place very rapidly, under these particular conditions, when quinine has not been given.

It cannot, however, be said that quinine has no effect upon the nervous system. As I have already stated, somewhat large doses distinctly tend to the production of sleep; but the diminished cerebral activity induced by quinine cannot be compared, in the slightest degree, with that resulting from morphine or other soporifics. The most that can be said of it is that it is sometimes a pleasant collateral effect of the drug.

The effect of quinine on the EXCRETION OF NITROGEN in the urine has often been investigated, both in febrile and in non-febrile conditions. The first investigation of this kind

[1] C. Binz, "Ueber die antipyretische Wirkung von Chinin und Alkohol," 'Arch. f. path. Anat.,' u. s. w., 1870, Bd. li, S. 6; Gottlieb, 'Arch. f. exper. Path. u. Pharm.,' 1890, Bd. xxvi, S. 449.

was with regard to the uric acid.[1] In almost every case the average amount excreted, within twenty-four hours, was reduced one half, and, in a subsequent investigation,[2] the reduction was still more considerable, and averaged about 95 per cent. This was not due to retention of the acid within the organism, but to a decrease of the amount formed, for when the administration of quinine was discontinued, no more uric acid was excreted than before the beginning of the experiment.

We now come to a series of experiments with regard to the excretion of urea. It might have been supposed that, considering the large amount daily excreted, the various investigators would soon have arrived at some uniform results. This, however, was by no means the case. I will not join in the controversy on this subject, but will merely point out that the exhaustive experiments of G. Kerner[3] showed that the amount of urea was distinctly decreased, the decrease, in fact, being proportionate to the dose of quinine. While, under normal conditions, the total amount of nitrogen in the urine was 18·33 grammes (275 grains), it fell to 16·17 grammes (243 grains), after 0·6 gramme (9 grains) of hydrochlorate of quinine, and to 13·98 grammes (210 grains) after 1·66 gramme (25 grains) had been given. The amount of sulphuric acid in the urine was also considerably reduced, and the figures showing the quantities of the various substances eliminated on the days when quinine was no longer taken, plainly show that the reduction was due to diminished formation of the products of metabolism, and not to their imperfect renal excretion. This much-disputed question was again examined, with every necessary precaution, by J. Prior.[4] The mean results of some experiments

1 H. Ranke, 'Versuche über die Ausscheidung der Harnsäure beim Menschen,' München, 1858.

2 H. V. Bosse, 'Der Einfluss von Arzneimitteln auf die Ausscheidung der Harnsäure,' Doctordissertation, Dorpat, 1862, S. 10—13.

3 G. Kerner, 'Arch. f. d. ges. Physiol.,' 1870, Bd. iii, S. 93 und 110.

4 J. Prior, "Ueber den Einfluss des Chinins auf den Stoffwechsel des gesunden Organismus," 'Arch. f. d. ges. Physiol.,' 1884, Bd. xxxiv, S. 237. On pp. 272—275 will be found a complete list of the publications on both sides of the question; see also M. Kumagawa, 'Arch. f. path. Anat.,' 1888, Bd. cxiii, S. 188.

upon himself are given in the following table, and corroborate those arrived at by Kerner.

Mean Results of Prior's Experiments.

No.	Quantity of urine in c.c.	Specific gravity.	Urea.	Uric Acid.	Sodium chloride.	Sulphuric acid.	Phosphoric acid.	Nitrogen in the fæces.
			Grms.	Grms.	Grms.	Grms.	Grms.	Grms.
1	1586	1020	39·76	0·74	18·64	2·50	3·68	0·67
2	1586	1020	39·60	0·74	18·74	2·51	3·51	0·94
3	1800	1017	32·70	0·12	17·10	2·00	3·17	0·43
4	1743	1017	33·07	0·22	17·02	1·65	2·90	0·51
5	1657	1019	34·00	0·41	17·75	1·74	3·09	0·83
6	1820	1018	28·10	0·07	15·93	1·24	2·12	0·93

No. 1 gives the daily normal amount of each substance previous to administering the quinine; No. 2, the amount on days subsequent to that on which quinine was given; No. 3, the amount after a single dose of 1·5 grammes (22½ grains); No. 4, after 1·0, 1·0, and 1·5 grammes (15, 15, and 22½ grains) on three consecutive days; No. 5, after repeated doses of 0·25 gramme (about 4 grains); and No. 6, after two doses of 2 grammes (30 grains) in one day.

This table shows very plainly that there was a decrease in the various urinary constituents proportionate to the dose of quinine. The increase in the quantity of urine is an interesting point. The author attributes it, and rightly, I think, to direct irritation of the kidneys from the quinine, which could be detected in the urine for three days after it had been taken. In this way the kidneys became acutely hyperæmic, and this condition was manifested by pain in the lumbar region and by the inclination to frequent and painful micturition.

The results of Prior's experiments upon a fasting dog, to which he gave 0·5—0·75 gramme of quinine in 200 c.c. of water, agreed entirely with those of experiments upon human beings on ordinary diet. They have a special value as excluding an objection which might possibly be raised; for they show that quinine does not prevent the absorption of albumen by the stomach and intestine, and that the decrease

of the products of its metabolism, excreted in the urine, is consequently not due to this cause. This objection had really been already disposed of by the small proportion of nitrogen in the fæces given in the above table; it was satisfactory, however, to have the point settled by experiments made when the stomach was empty.

Similar results were obtained almost at the same time from FEVER PATIENTS.[1] In every case of exanthematous typhus and recurrent fever, in which the points were investigated, the metabolism of nitrogenous matter in the organism, and the excretion of phosphates in the urine, were reduced by the action of quinine. The quantity of urine was increased. The nitrogen, and other constant ingredients of the milk given as nourishment, were more readily absorbed, when quinine was given, than without it. Sodium salicylate produced a similar effect to quinine; the cold bath was more efficacious than either.

The results of the investigations, therefore, show that quinine, among other effects, checks OXIDATION OF THE TISSUES and also ALBUMINOUS METABOLISM. There is also a synthetic process which is retarded by quinine. If blood containing a certain amount of glycocoll and benzoic acid is caused to circulate through a recent kidney, during the process these two substances are transformed into hippuric acid. But if 0·5 per cent. of hydrochlorate of quinine be added, the formation of hippuric acid is lessened, and falls to about one sixth, and still lower if a larger quantity of quinine is used.[2]

There are other facts which indicate that the antipyretic action of quinine is independent of its effect on the nervous system. According to Mosler[3] and Landois, quinine causes contraction of the spleen, even if all the nerves in connection with it are severed. The diminished reflex irritability which

[1] N. A. Sassetsky, "Der Einfluss fieberhafter Zustände und antipyretischer Behandlung auf den Umsatz der stickstoffhaltigen Substanzen," 'Arch. f. path. Anat.,' 1883, Bd. xciv, S. 485. (From the clinic of Manasseïn at St. Petersburg.)

[2] Schmiedeberg u. A. Hoffmann, 'Arch. f. exper. Path. u. Pharm.,' 1877, Bd. vii, S. 243.

[3] Mosler, 'Die Pathologie und Therapie der Leukämie,' 1872, S. 251.

is said to be produced by quinine, and has been regarded by some as one of its most important effects, has merely been demonstrated upon frogs, and upon them only with doses which produced fatal results, when naturally there is an end to all vital actions, reflex irritability among the rest.[1]

All these results tend to prove the accuracy of the view which I have long advanced, namely, that quinine in non-poisonous doses reduces the temperature not only in healthy individuals, but still more in certain continued fevers, by directly inhibiting the action of those cells which are concerned with metabolism.

I will now pass over any further investigations which have been made by myself and others, and, leaving scientific considerations on one side, turn to those of a PRACTICAL NATURE, which have a pharmacological bearing. I will proceed to discuss, in the first place, the action of quinine on the stomach and intestines.

Generally speaking, quinine does not disturb the digestive function; on the contrary, it alone, of all the alkaloids which have been tested in this respect, is efficacious, when given in small doses, as a stimulant to gastric digestion.[2] The vomiting, which unquestionably often follows its use, may

[1] H. Heubach, "Beiträge zum Pharmakodynamik des Chinins," 'Arch. f. exper. Path. u. Anat.,' 1875, Bd. v, S. 1. (From the Pharmacological Institute in Bonn.) Lauder Brunton and G. Pardington, 'St. Bartholomew's Hospital Reports,' 1876, p. 150. Evidence is here brought forward to prove that the results, so frequently quoted, of Chaperon's experiments ('Arch. f. d. ges. Physiol.,' 1869, Bd. ii, S. 293) depended entirely upon the sulphuric acid which had been added in excess to dissolve the SULPHATE of quinine.

My observations upon the effects of quinine have been made exclusively with the HYDROCHLORATE, which has a neutral or slightly basic reaction, and is easily soluble in water without the addition of any acid.

[2] L. Wolberg, 'Arch. f. d. ges. Physiol.,' 1880, Bd. xxii, S. 306.

proceed from one of three causes. First, its bitter taste which has a nauseating tendency; secondly, the choice, when the normal amount of hydrochloric acid in the stomach is defective, of a salt which is not readily soluble; thirdly, the action of the drug upon the brain. The first two causes, if known, can be easily avoided by the physician; and the last also, if the dose given to a sensitive patient is not too large to begin with. The brain soon becomes tolerant of its action. It is well to tell the patient, that the first dose may possibly cause vomiting; but that is no reason against taking a second, for it will only cause slight nausea, and after the third no unpleasantness of this kind will be felt. In whooping-cough the violent attacks of vomiting are rendered less frequent by quinine, and quickly cease altogether as the other symptoms improve.

Cinchonism, or quinic intoxication, to which reference is frequently made, when produced by large doses, usually commences with some deafness, buzzing and ringing in the ears, nausea, weariness of the limbs, retching, vomiting, and drowsiness.[1] Of course, if the dose is large enough, symptoms may arise which result from paralysis of the nervous centres. Life may be maintained for a considerable time by artificial respiration, but at last the heart becomes paralysed and ceases to beat. Stimulation no longer excites the slightest contraction, and it might be supposed that the poisoning was due to digitaline. Such, at least, has been the condition which I have noted in animals.

A man aged forty-five who was suffering from constipation, took by mistake a single dose of 3 drachms (12 grammes) of quinine sulphate, instead of cream of tartar. An hour afterwards he had pain in the head and stomach, dizziness, loss of power and unconsciousness. His face was pale, his lips and also his limbs were blanched and cold; the pulse equable, slow, and hardly perceptible; the respiration infrequent, the pupils widely dilated; there was almost complete loss of sight and hearing, even after consciousness returned. The doctor[2]

[1] For the effect of quinine on the healthy subject see Hugo Schulz, 'Arch. f. path. Anat.,' 1887, Bd. cix, S. 21.

[2] Giacomini, 'Annali universali di med.,' 1841, vol. xcvii, p. 389.

who saw him eight hours after the dose had been taken ordered his whole body to be wrapped in warm blankets, some parts to be rubbed, and stimulants to be given internally. After a few hours there were signs of improvement, which progressed steadily throughout the following day, but even on the fifth day the patient was unable to leave his bed for more than half an hour. There was some improvement in his general condition as well as in his sight and hearing, but it was "a long time" before complete recovery took place.

In severe cases of quinine poisoning artificial respiration should be among the remedies employed, with rhythmical pressure on the region of the heart, so as to maintain its action by a strong mechanical stimulus. Hot baths (39° C. = 102·2° F.) with cold effusion should also be tried. Strong hot coffee or tea may be given, and atropine would also probably prove of service. Moreover the physician should in all cases, before giving large doses of quinine, take special care to ascertain that there are no symptoms of CARDIAC or PULMONARY WEAKNESS, as any such condition would contra-indicate the administration of a large dose. Death has not unfrequently occurred in patients suffering from typhoid fever after the administration of 2 grammes (60 grains) of quinine,[1] and even half that amount may produce dangerous results. The largest dose, therefore, should not exceed 0·5 gramme (7½ grains), and in the intervals between the doses, some alcoholic stimulants will be necessary.

Having just referred to the susceptibility of THE HEART to the action of quinine, I may here mention that moderate doses slightly stimulate that organ, acting probably on its muscular tissue. The vagus takes no part in this action; it is only from large doses of quinine that the vagus becomes slightly paralysed, but the effect produced is in no way to be compared with that caused by atropine.[2]

The DEAFNESS and other aural troubles, as a rule, only last for a few hours or days, though in some instances serious results have been produced.[3]

[1] Husemann, 'Beiträge zur Chinin vergiftung,' 1888, S. 7.
[2] C. Binz, 'Arch. f. exper. Path. u. Pharm.,' 1875, Bd. v, S. 46.
[3] Schwabach, 'Deutsche med. Wochenschr.,' 1884, S. 163.

In one case, a man aged thirty-seven, suffering from fever, took a single dose of 1·2 grammes (18 grains) of hydrochlorate of quinine. The fever was cured, but he was immediately seized with loud tinnitus aurium, pain in the left ear, oppression in the head, attacks of dizziness, and extreme deafness. With the left ear the ticking of a watch, and the note of a tuning-fork held against the cranium were quite inaudible. By the administration of 5 grammes (75 grains) of sodium salicylate (?) in five hours all the symptoms were intensified. After treatment of the ear symptoms for some months the patient's condition was only partially improved; he could hear a little better, but still only indifferently.

I may here state that some interesting results have been furnished by experiments on the HEALTHY HUMAN EAR.[1] In twelve experiments, after the administration of 1 gramme (15 grains) of hydrochlorate of quinine, the temperature of the external meatus fell, on an average, 0·56 of a degree within from two to two and a half hours. The external meatus and the tympanum were not hyperæmic; on the contrary, they became pallid under the full action of the quinine. This may not be the case always; in some individuals the quinine might, with equal probability, cause inflammation of the tympanic cavity, and in others again, those inflammatory affections of the outer skin to which I shall presently refer. In fact, inflammatory extravasations in the semicircular canal and in other parts of the inner ear have been artificially set up in a cat by the administration of quinine. From my own observation I know that cats are very sensitive to the action of quinine, but it is only in very exceptional cases that any lasting injury to the auditory apparatus of human beings is caused by the action of quinine.

Disturbed vision has frequently been noted after large doses of quinine. It results from direct paralysis of the optic nerves, and not from any opacity of the refracting

[1] P. Guder, 'Experimente ueber die Chininwirkung, insbesondere auf das gesunde menschliche Gehörorgan," Berlin, 1880, Doctor-dissertation unter Leitung von Weber-Liel; W. Kirchner, 'Berl. klin. Wochenschr.,' 1881, No. 49; "Extravasate im Labyrinth (bei Tieren) durch Chinin und Salicylsäure," 'Monatschr. f. Ohrenheilk.,' 1883, ref. 'Centralbl. f. d. med. Wiss.,' 1883, S. 665.

media. Von Graefe has given an account of two instances,[1] both in patients suffering from malarial fever. One patient had taken in the course of several weeks 21·6 grammes (about 330 grains) of quinine; the other had taken 30 grammes (450 grains). The former had impaired vision, the other complete loss of sight, and in both the defect continued for several months. Recovery took place gradually and spontaneously, and seemed to be promoted by abstracting blood from the temples. The following is a more recent case:[2]

A woman thirty-five years of age had a miscarriage with symptoms of septic endometritis. Cold douches and quinine were employed to reduce the fever, 4·8 grammes (nearly 75 grains) of the latter being given in thirty hours. An eclamptic seizure ensued, followed immediately by total loss of sight and hearing. There was no albumen in the urine; the pupils of the eyes were widely dilated and motionless, the refractive media clear, the retina almost bloodless and insensitive to bright concentrated light; consciousness returned the day following the attack, and was not subsequently affected. The hearing returned within a few days. The affection of the peripheral parts of the retina was permanent, but the central part slowly recovered its function in about six months, and there was still some colour-blindness, which was absolute when the sight first returned.

Numerous cases, however, have been reported[3] which tend to show that disturbances of vision, following the administration of quinine, may be due not necessarily to the remedy, but largely to the disease itself, and cannot rightly be attributed to the remedy.

Temporary AFFECTIONS OF THE SKIN are very common results after taking quinine. They usually appear in the form of eczema, roseola, erythema, urticaria, or purpura. Here are a few illustrations. Four cases of purpura

[1] Von Graefe, 'Arch. f. Ophthalmol.,' 1857, Bd. iii, S. 396.

[2] E. Gruenig, "On Quinine Amaurosis," 'Arch. of Ophthalmol.,' 1881, vol. x, p. 81. Other cases are also reported, but they were apparently less severe. See also 'Centralbl. f. d. med. Wiss.,' 1882, S. 425; 'Centralbl. f. klin. Med.,' 1880, S. 575; Garofalo, ibid., 1890, S. 789.

[3] M. Landsberg, "Sehstorüngen durch Intermittens," 'Arch. f. Augenheilk.,' 1884, Bd. xiv, S. 87.

hæmorrhagica have been reported,[1] in which the most remarkable feature was, that the effect was produced by small doses, such as 0·1 to 0·15 gramme (1½ to 2¼ grains) every six hours. According to another medical report,[2] a lady forty years of age had œdema of the face and limbs, and a well-developed erythematous rash, followed by desquamation, after taking quinine. An intentional repetition of the dose caused a repetition of the symptoms. As far back as 1871 I briefly referred to these and similar cases in a paper which I published on the subject.[3]

The KIDNEYS and URINARY PASSAGES are not insensitive to the action of the alkaloid, as was shown by Prior's experiments. In large quantities it may occasion albuminuria and catarrhal inflammation of the bladder. An attack of the latter, accompanied by severe fever, was induced by the administration of 4 grammes (60 grains) in the course of the day.[4] The patient was an old man who was suffering from chronic cystitis, and to whom for other reasons the quinine was given. Cases have also been reported in which a few decigrammes of quinine have caused hæmaturia, jaundice, and fever,[5] apparently quite unconnected with the malarial disorder for which it had been prescribed. These effects are less surprising than the skin eruptions which sometimes follow the administration of quinine, since most of the quinine, which is eliminated from the system, passes off by the kidneys.

[1] W. H. Vipan, "Quinine as a Cause of Purpura," 'Lancet,' 1865, ii, 37. These four cases are the same as those referred to in the 'Gaz. des hôpit.,' 1867, p. 31, but with different names, dates, and addresses, and under these they have been quoted by subsequent writers.

[2] Garraway, 'Brit. Med. Journ.,' 1869, ii, p. 388.

[3] C. Binz, "Beobachtete Nachteile grosser Geben Chinin," 'Deutsche Klinik,' Berlin, 1871, S. 409; H. Köbner, 'Berl. klin. Wochenschr.,' 1877, S. 329; 1877, S. 205 und 325; O. v. Heusinger, ibid., S. 361; Pflüger (Bern.), ibid., S. 547; Denk, 'Wien. med. Wochenschr.,' 1880, S. 946.

[4] Briquet, 'Traité de Quinquina,' 1855, p. 229, where other cases are also reported.

[5] S. Tomaselli, 'La intossicazione chinica e l' infezione malarica,' Catania, 1874. Further observations are reported in a second paper, published in 1877. G. Karamitsas, 'Bull. gén. de thérap.,' 1879, vol. xcvii, pp. 53, 108, et 149.

In referring to the elimination of the remedy, I must not omit to mention some peculiarly interesting facts with regard to it. Kerner[1] recovered from the urine 80, 95, and 96 per cent. of the quinine which had been administered. The excretion of HYDROCHLORATE of quinine began fifteen minutes after it had been taken, was most copious (30 per cent.) in the twelfth hour after, and lasted till the forty-eighth hour, when 1 per cent. was still to be found. SULPHATE of quinine did not appear in the urine for forty-five minutes, and 1 per cent. of it was still to be found in the urine passed in the sixtieth hour after taking it. The greater part of the quinine passes off in an amorphous form, a small part of it being converted by oxidation into a substance which Kerner described as dihydroxyl-chinin. It has then lost all the properties of quinine with which we are concerned.

Miscarriage and premature labour are said to be induced by quinine. After an exhaustive examination of the publications on this subject, it appears to me that these effects simply result from the morbid conditions for which the remedy is given.[2] In proof of this we find it actually recommended as a preventative against abortion.[3] In a case in which 1·5 grammes (23 grains) of sulphate of quinine was given to the mother at the commencement of labour no particular harm accrued to the infant.[4] What truth there may be in the statement that small doses of quinine, taken daily for a considerable time at the beginning of pregnancy, cause abortion, is a matter that requires closer investigation.

In recent years several cases of the so-called inverted action of quinine have been reported—cases, that is to say, in which its use was followed by a rigor with subjective heat and rise of temperature, without inflammation of any organ being apparent.[5]

[1] G. Kerner, loc. cit., Bd. iii, S. 123 und 160.

[2] Cf., among others, Bailey, ref. 'Centralbl. f. d. med. Wiss.,' 1873, S. 304; de Ranse, 'Gaz. méd. d. Paris,' 1874, p. 529, and Sistach, ibid., p. 584; R. Neale, 'Practitioner,' 1880, vol. xxiv, p. 170.

[3] Campbell, ref. 'Centralbl. f. Gynäk.,' 1883, S. 146.

[4] M. Runge, ref. 'Centralbl. f. d. med. Wiss.,' 1880, S. 416.

[5] Leichtenstern, 'Deutsche med. Wochenschr.,' 1884, S. 849;

An increase of general reflex irritability is described as one of the exceptional effects of quinine.[1] In epileptic patients the attacks are said to increase in frequency under its influence. We may also include here a case of violent mental derangement which occurred in a man after the administration of 13·5 grammes (about 200 grains) of chinoidine within about twelve hours.[2]

Quinine has been used externally in many ways and with good results on account of its strong antiseptic properties,[3] nor has it seemed to produce any injurious collateral effects. Repeated friction of the healthy skin with quinine ointment makes it chapped and sore.

The officinal preparations are—

1. Cortex Chinæ, Cortex Cinchonæ, cinchona bark, preferably that of the *Cinchona succirubra*. It is the bark of the stem and branches reduced to a reddish-brown powder, and should contain at least 5 per cent. of alkaloids. The most useful form is a decoction (5—10 to 150) in distilled water with a few drops of hydrochloric acid. Most of the cincho-tannic acid of the cinchona is converted in the process into the insoluble cinchona-red.

2. Extractum Chinæ Aquosum, prepared with cold water and without any alcohol. A thin, reddish-brown extract, forming an opaque solution with water. It contains little quinine, its chief ingredients being a bitter extract, which we shall discuss later, and tannin. It is employed to stimulate the digestion and nutrition, in doses from 0·1 to 0·5 gramme (1½ to 7½ grains) as pills, two or three times a day.

3. Extractum Chinæ Spirituosum, prepared by maceration in diluted alcohol. A dry, reddish-brown extract, forming an opaque solution with water. It contains a large but

G. Merkel, 'Arch. f. klin. med.,' 1885, Bd. xxxvi, S. 356; Herrlich, 'Charité-Annalen,' 1885, Bd. x, S. 232.

[1] A. Erlenmeyer, 'Centralbl. f. Nervenheilk. u. Psychiat.,' 1890, June number.

[2] R. Marcuse, Doctordissertation, Berlin, 1891. From the West Prussian provincial lunatic asylum at Kortau.

[3] C. Binz, "Das Chinin als äusseres Heilmittel," 'Deutsche med. Wochenschr.,' 1877, p. 525. Instructive cases (Samelsohn, Struck, and Beneke) of septic keratitis, cancerous ulceration, and hospital gangrene.

variable amount of quinine, and is therefore not a reliable preparation for serious disorders. It is employed for the same purposes as the previous extract.

4. Tinctura Chinæ, tincture of cinchona, one part of cinchona bark macerated in five parts of proof spirit—is reddish brown and very bitter. The dose is from twenty to thirty drops.

5. Tinctura Chinæ Composita,—cinchona bark, orange peel, gentian root, and cinnamon macerated in proof spirit. Reddish brown, aromatic, very bitter, smells of cinnamon and orange peel. The dose is from twenty to thirty drops.

Of the alkaloids of cinchona bark, quinine is the only one in general use. The following salts are officinal:

(1) Chininum Sulphuricum, Quininæ Sulphas, basic sulphate of quinine $(C_{20}H_{24}N_2O_2)_2,H_2SO_4 + 7H_2O$. White, silky, filiform crystals, with a bitter taste and a neutral or slightly alkaline reaction. Soluble in 800 parts of water or 90 parts of alcohol. In ague and similar disorders it is given in doses of 0·5 to 1 gramme (7½ to 15 grains) during the intervals of the fever; in other diseases it may be given in doses of 0·1 to 0·25 gramme (1½ to 4 grains) every two hours, or twice a day in doses of 0·5 gramme (7½ grains) or more.

The sulphate of quinine was the form in which the alkaloid was first obtained, and this salt was consequently the one generally prescribed; but it is not a useful preparation, as, owing to its comparative insolubility, when given in the form of powder or pills with water it often causes discomfort in the stomach, and fails to be absorbed with sufficient rapidity or completeness. If an aqueous solution is prescribed, some acid should be added to it; hydrochloric acid is the best, as it tends to promote gastric digestion, and the solution is far less likely to become mouldy than when sulphuric acid is added. It is unnecessary, however, to add an acid to solutions of Chininum Bisulphuricum, bisulphate of quinine—

$$C_{20}H_{24}N_2O_2.H_2SO_4 + 7H_2O,$$

as this is easily soluble in water. The solution even when largely diluted has a beautiful bluish tint or fluorescent appearance, resulting from the absorption of the ultra-violet rays, and the emission of the blue rays. The salt consists of white shining prisms, which are soluble in eleven parts of

water or thirty-two of alcohol. The solution is very apt to become mouldy. The salt contains one molecule of the alkaloid and one of the acid, and is therefore, properly speaking, a neutral salt, but it has an acid reaction.

The solution of the following salt, if not contaminated with sulphuric acid, has a slightly basic reaction, and does not become mouldy.

(2) CHININUM HYDROCHLORICUM s. MURIATICUM, Quininæ Hydrochloras, hydrochlorate of quinine—

$$C_{20}H_{24}N_2O_2.HCl + 1\frac{1}{2}H_2O,$$

consists of white, filiform crystals soluble in 34 parts of water, and in 3 of alcohol. If the quinine is given in the form of a powder, this preparation is preferable to the sulphate, on account of its being more readily dissolved in the stomach.[1] It also contains a rather larger proportion of the active principle, 83·6 per cent. as compared with 74·3 per cent. in the sulphate.

(3) CHININUM FERRO-CITRICUM, Ferri et Quininæ Citras, citrate of iron and quinine. This consists of bright translucent scales of a deep reddish-brown colour, which have a bitter, ferruginous taste, dissolving in water slowly but in all proportions, not readily soluble in alcohol. It is used only as a bitter and ferruginous tonic, especially in cases of anæmia, and may be prescribed in doses of 0·1 to 0·5 gramme (1½ to 7½ grains) two or three times a day. Its composition is not uniform, but it should contain at least 9 per cent. of quinine.

If quinine, particularly when in solution, is exposed to sunlight, it first turns yellow and then brown. The same change in the alkaloid also takes place, to some extent, in the outer layers of the living bark. This gives rise to the amorphous modification[2] of quinine, which cannot again be changed into the crystalline form. It is called QUINOIDINE or

[1] C. Binz, "Vier Fälle von sporadischem Wechselfieber," 'Deutsche Klinik,' 1867, S. 217.

[2] Liebig, 'Ann. d. Chemie,' 1846, Bd. lviii, S. 353; O. Diruf, 'Untersuchungen über das Chinoidin,' Erlangen, 1850; G. Kerner, loc. cit.; Hagens, "Chinoidum citricum" (Jobst), 'Zeitschr. f. klin. Med.,' 1883, Bd. v, S. 242; Finkler und Prior, "Chininum amorphum boricum" (C. Zimmer), 'Deutsche med. Wochenschr.,' 1884, S. 81.

CHINOIDINE, and in former times, when the price of crystalline quinine was very high, was often substituted for the latter. It has much the same effect.

There is often, on account of its extreme bitterness, great difficulty in giving quinine to infants, and yet in some cases it is often a most efficient remedy. For example, most cases of uncomplicated WHOOPING-COUGH can be cured in about a fortnight if the child can be induced to take daily as many decigrammes (1½ grains) as its age in years. The amount given in one day, however, should not exceed 1·5 grammes (23 grains). With a child under a year old the treatment should commence with as many centigrammes as its age in months.[1] The vomiting first abates, then the number and presently the violence of the paroxysms, and the case is transformed into one of simple bronchial catarrh. The bronchitis, or broncho-pneumonia, which so often accompanies whooping-cough can generally be prevented or cured by quinine.

For cases in which the hydrochlorate is refused, but in which the use of quinine is likely to prove of great service, we may have recourse to the following officinal preparation:

(4) CHININUM TANNICUM, tannate of quinine, a yellowish-white, amorphous and odourless powder, with a faintly bitter and very slight astringent taste, containing 30 to 32 per cent. of quinine. The absence of taste is due to the fact that it is very slightly soluble either in water or in the saliva. It can easily be given to children in syrup or

[1] This method of treatment was first suggested by myself, and described in the 'Jahrb. f. Kinderheilk.,' Leipzig, 1868, i, S. 233. Since then much corroborative testimony as to its efficacy has appeared, some of it from England,—see Dawson, 'The Practitioner,' 1873, p. 378, amongst others. The bibliography of the subject has been collected by B. Fervers, 'Jahrb. d. Kinderheilk.,' 1888, Bd. xxviii, S. 117. The most recent and exhaustive corroboration comes from E. Ungar, 'Deutsche med. Wochenschr.,' 1891, No. 18; P. Baron, 'Berl. klin. Wochenschr.,' 1893, No. 48; and H. Laubinger, 'Jahrb. d. Kinderheilk.,' 1895, Bd. xxxix, S. 141. It is easy to prescribe a bitter medicine like quinine for children, but by no means easy to induce them to take it. It requires great tact, patience, and perseverance,—three qualities which are not possessed by every practitioner, and the lack of which naturally leads to negative results.

something similar. But, on the other hand, it possesses disadvantages: 1st, it is not so quickly absorbed by the intestinal canal as the hydrochlorate; and 2ndly, it contains less than half the quantity of quinine. The first may be counteracted, to some extent, by giving after the dose a small quantity of light wine, in which the tannate of quinine is more readily soluble; and the second by giving a larger dose.

Quinine cures whooping-cough, not by repressing the fits of coughing or diminishing their intensity, as is the case with purely sedative remedies; but, as the mode of convalescence shows, by lessening the exciting cause, which is undoubtedly a microbe. Large doses are absolutely necessary in this disease, but experience has taught us that quinine is generally very well borne in childhood,—much better, in fact, than in later life, when it readily produces those effects on the brain to which I have already called your attention.

The tannate of quinine is not nearly so efficient as the hydrochlorate; it is a makeshift. Care should therefore be taken that the percentage of quinine in it does not fall below that above mentioned. The German Pharmacopœia gives a simple test for determining the proportions, which can be readily applied in doubtful cases.

The preparations of quinine sometimes contain IMPURITIES, due either to their careless manufacture, or to their being purposely adulterated. The latter was done, in a wholesale manner, by an army contractor in Berlin in 1866, by another in Tiflis in 1878, and by a Parisian merchant in 1883.[1] The possibility of this must, therefore, not be overlooked by the physician. The official Pharmacopœia contains full directions for determining the purity of a specimen, and for detecting the presence of any of the other cinchona alkaloids (the commonest form of adulteration, owing to their price being less) or foreign matter (such as plaster of Paris, calcined magnesia, or powdered starch). Now, however, that the price is so much lower, direct adulteration is probably less common than formerly.

Since quinine has fallen to a price which is within the

[1] 'Gaz. des tribunaux,' June 25th, 1883.

reach even of the poor, the use of the other alkaloids of cinchona bark—quinidine, cinchonine, and cinchonidine—which were occasionally employed therapeutically, and which possess similar properties to quinine, though much feebler in degree, has become unnecessary.

The bitter extract in cinchona bark, QUINOVINA, has also a certain amount of importance. Crude quinovine is a secondary product, in the extraction of quinine. When pure, it is an amorphous, resinous substance, with a faint balsamic odour and neutral reaction. It is only slightly soluble in boiling water, but more soluble in alcohol, ether, and ethereal oils. Its formula is $C_{30}H_{48}O_8$. If to its alcoholic solution anhydrous hydrochloric acid is added, it absorbs a molecule of water, and is resolved into quinic acid and glucose; it belongs, therefore, to the glucosides. Quinovine is readily soluble in proof spirit; quinic acid is comparatively insoluble, This acid was first discovered in the *Cinchona nova*. It is also contained in tormentilla root, the *Potentilla tormentilla*, which in old times had the reputation of being an excellent diuretic in many forms of dropsy.[1]

QUINO-TANNIC ACID.—This preparation precipitates lime, albumen, &c., in the same way as gallo-tannic acid does. With oxide of iron it gives a dark green precipitate, instead of the dark blue caused by the latter. By heating with diluted acids it is resolved into cinchona-red—to which the formula $C_{28}H_{22}O_{14}$ has been given—and glucose. The red colour, characteristic of many kinds of cinchona bark, is due to the presence, in a natural state, of this colouring matter. The tannin in cinchona bark may possibly have the same action upon the human organism as the tannin of galls, but in the case of cinchona-red such a supposition is almost excluded by the different reactions which it gives, and by its comparative insolubility. To secure the benefit of the cincho-tannic acid the infusion of the bark must be prepared with cold water, for in the decoction the greater part of it is transformed into cinchona-red and precipitated.

In the ADMINISTRATION of quinine, I would again remind you that the sulphate should, on account of its insolubility,

[1] G. Kerner, "Ueber den therapeutischen Wert der Chinovasäure," 'Deutsche Klinik,' 1868, S. 81.

be altogether discarded. It possesses no advantage whatever over the hydrochlorate of quinine, and has the disadvantages to which I have already referred. Nothing but the *vis inertiæ* of the medical profession has allowed it to retain a place in the Pharmacopœia.

When hydrochlorate of quinine cannot be given by the mouth, it may be administered either hypodermically or by the rectum or the veins. After various unsuccessful attempts to arrive at a form in which quinine could be subcutaneously injected without causing unpleasant after-effects, the following solution has been found efficient:[1]—hydrochlorate of quinine 10 grammes (150 grains), distilled water 7·5 grammes (112½ minims), officinal hydrochloric acid 2·5 grammes (37½ minims). Every cubic centimetre (15 minims) of this solution, which is of a pale yellow colour and has an acid reaction, contains about 0·75 grammes (11¼ grains) of the salt. It is remarkable that the subcutaneous injection of this solution in the dorsal region causes no more pain than that which results from the slight puncture. In Bonn it has very rarely led to redness, swelling, abscesses or sloughing of the skin, in the children to whom it has been administered subcutaneously. That it is thoroughly absorbed, is shown by the satisfactory results which have been produced.

From experiments which have been made on the delicate skins of children,[2] it appears that cutaneous inunction with quinine, which has often been, and is still occasionally employed, does not lead to its absorption. Enemas have the drawback that the medicine is often quickly returned with the liquid; nevertheless in some acute cases they must be tried. Quinine suppositories have been strongly recommended;[3] 1·5 grammes (23 grains) of HYDROCHLORATE of quinine are mixed with 2 grammes (30 grains) of melted cacao butter, and inserted into the rectum, after this has been previously washed out. The antipyretic effect manifests

[1] Vitali and Galignani (Piacenza), 'Annali Univers. di Med.,' 1872, July 14th.

[2] G. Primavera, "Nuovo esperimento sulle frizioni di solfato di chinina, con lo scopo di videre se si assorbi dai bambini," 'Il Morgagni' (Naples), 1869, p. 93.

[3] R. Pick (Coblenz), 'Deutsche med. Wochenschr.,' 1884, S. 277.

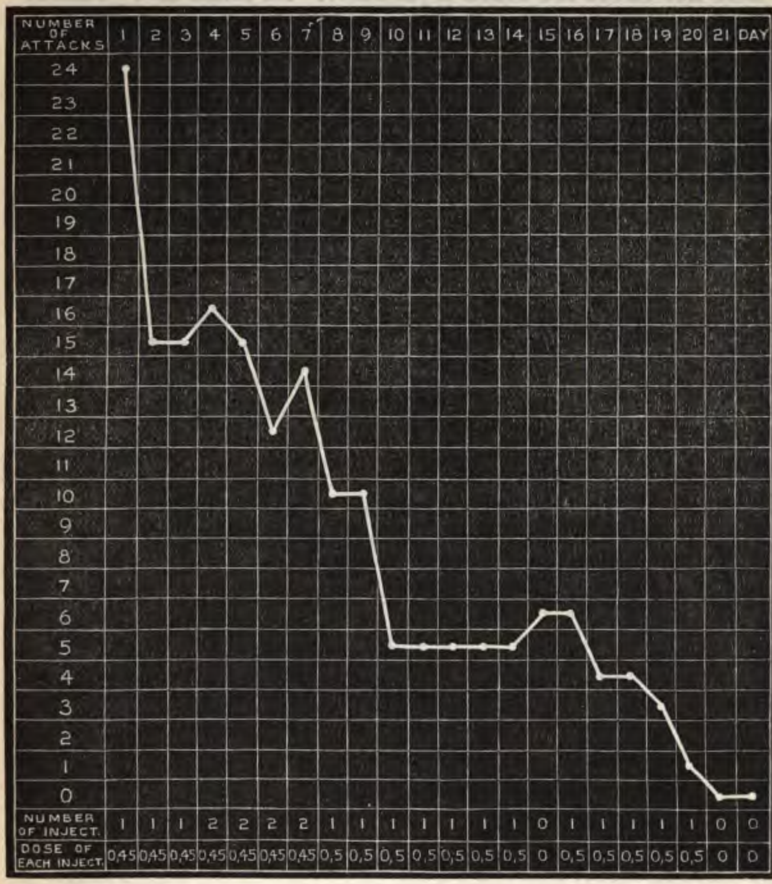
itself in young children, of nine months and upwards, in a few hours, and the temperature during the night may fall from 40·8° to 38·4° (105·4° to 101·1° F.) or so. This occurred in cases of bronchitis, pharyngitis, and broncho-pneumonia. The plan seems worth trying when there is much difficulty experienced in giving quinine to children, owing to the vomiting which it causes. The suppository, though it may be passed up as far as possible with the finger, will remain, as a rule, only one hour, or at most, not longer than three hours in the rectum.

Some experiments have very recently been made with subcutaneous injections of the acid hydrochlorate of quinine, Chininum Bimuriaticum, which have been followed by satisfactory results. This salt consists of fine colourless crystals, which dissolve at the ordinary temperature in less than their own weight of distilled water, and form with it a pale yellow syrupy liquid. The composition of the salt is $C_{20}H_{24}N_2O_2.2HCl$. The solution has a strong acid reaction, but, like the one previously mentioned, it causes little or no pain when injected in the less sensitive parts of the skin, and as a general rule produces no irritation and is quickly absorbed. H. Laubinger, in his report already quoted, which was drawn up under the direction of Professor Ungar, refers to this preparation. I here reproduce (see next page) one of the twelve charts illustrating his report. The patient was a girl of seven, who had suffered for four weeks from whooping-cough which had already reached the convulsive stage. Vomiting was constant, and the mucus was sometimes tinged with blood. Before the quinine was prescribed the paroxysms numbered twenty-four in twenty-four hours, and were very violent. The further progress of the case is shown on the subjoined chart.

The following formula may be employed with advantage:—
℞ Chinin. Bimuriatic. 10·0 (grana cl) solve in Aquæ Destill. 32·0 (℥j). Filtra. D. in vitro epistom. vitr. clauso. S. suo nomine. When prepared in this way the solution measures exactly 40 c.c. (ʒx), and each c.c. (15 minims) contains 0·25 (3¾ grains) of the salt [or one grain in four minims].

Stronger solutions are liable to irritate the skin. It is important, moreover, that the injection should be dexterously

performed, and without causing further injury to the skin than the fine puncture produced by the needle. If the



injection is made by passing the needle parallel to the surface of the skin, this method will almost infallibly give rise to ulceration.[1]

Direct injections into a vein in the forearm[2] have been made with the following solution : hydrochlorate of quinine, 1 gramme (15 grains) ; sodium chloride, 0·75 gramme (11¼

[1] On the subject of subcutaneous injection of bimuriate of quinine, see also O. v. Fleischl, 'Fortschritte d. Medizin,' 1895, No. 4, S. 145.

[2] G. Baccelli, 'Berl. klin. Wochenschr.,' 1890, S. 489.

grains); distilled water, 10 grammes (150 minims). This solution when lukewarm is perfectly clear, is readily borne, and does not affect the blood injuriously. As much as 1 gramme (15 grains) of the hydrochlorate has been given at once, but 0·4 or 0·6 (6 to 9 grains) was the usual amount. Only after single doses of from 30—80 cg. to 1 gramme (5 to 15 grains) were there in three instances any of the characteristic symptoms of quinine intoxication, such as a bitter taste in the mouth, dizziness, faintness, the pulse becoming at first smaller and less frequent, and then fuller and slower, tinnitus aurium, laboured respiration, and coldness of the skin. These symptoms generally passed off in from fifteen to twenty minutes. In one patient only, who was already much reduced by continuous fever due to malarial infection, did it happen that the weakness of the heart lasted so many hours as to necessitate the administration of cardiac stimulants.

Baccelli estimates that after giving 1 gramme (15 grains) of quinine, the blood contains 1 part of it in 5000—quite sufficient, as results prove, to paralyse any malarial amœbæ which it may contain.

To administer the remedy in this way, however, requires considerable dexterity, and is an operation not entirely devoid of danger. It should, therefore, not be resorted to, until all other methods have failed.

XXIV.

Salicylic acid—Its origin—Similarity in its general effects, to those of quinine—Sodium salicylate—The changes which it undergoes in the system—Elimination of the acid in the urine—Its effect upon metabolism—Drawbacks to its use—Officinal preparations—Salicin—Benzoic acid—Antipyrin—Thallin—Acetanilide or antifebrin—Phenacetin.

THAT quinine is a useful antipyretic remedy, which could be very extensively applied, was demonstrated very soon after the introduction of the clinical thermometer in 1861. If a patient who was suffering from continuous fever had his temperature lowered by the careful administration of a suitable dose of quinine, he felt less ill and exhausted, and had a steadier pulse, quieter respiration, and more tranquil sleep. This improvement in the general condition of the patient was formerly considered to be due to the tonic (from τείνω = I brace) action of the quiniue. It is now evident that the remedy temporarily removes or attenuates the cause which leads to the illness or exhaustion.

Until the year 1874, quinine was the only remedy in general use as an antipyretic, with the exception of cold baths and of alcohol, which had so far been proved, under certain conditions, to possess antipyretic qualities. It was discovered about this date that salicylic acid, $C_6H_4.OH.COOH$, has a similar antipyretic action.

Chemists had long been aware of the existence of salicylic acid in the oil of *Gaultheria procumbens,* or winter-green; in the leaves of our native *Spiræa ulmaria,* or meadow-sweet; and in those of *Monotropa hypopitys,* or yellow bird's-nest.

The name salicylic acid was given to it from the fact that it could be easily prepared from salicin, a bitter principle found in willow bark. Its relationship to carbolic acid led to its being artificially prepared from that substance, and Kolbe, of Leipzig, invented a cheap method by which this could be accomplished. It consists in heating carbolic acid and caustic soda in a stream of carbonic acid:

$$\underset{\text{(Carbolic acid)}}{C_6H_5OH} + \underset{\text{(Caustic soda)}}{NaOH} + CO_2 = H_2O + \underset{\text{(Sodium salicylate)}}{NaC_7H_5O_3}.$$

The latter salt is easily decomposed by sulphuric acid, the salicylic acid being thereby liberated. Kolbe called attention to three of its properties: that it is strongly antiseptic, that it is not poisonous to human beings, and that it passes, to a certain extent, unchanged through the body,—qualities which quinine also possesses. He therefore assumed that, like quinine, it must also have an antipyretic action—an assumption which experimental investigation in the main confirmed.[1]

The general effects produced by salicylic acid are, in every respect, so like those of quinine, that one account may readily serve for both substances. Small doses, such as 0·25 to 0·5 gramme (4 to 7½ grains) for adults, produce no marked effect. Kolbe took himself and gave to other persons 1·0 to 1·5 grammes (15 to 23 grains) a day, in some cases for nine months together, without apparent injury. Larger doses cause giddiness, stupor, singing in the ears and deafness, a feeling of weariness in the limbs, vomiting, and slightly diminished temperature; very large doses produce unconsciousness, infrequent respiration consequent on diminished excitability of the vagus, slowing of the pulse, diminished blood-pressure from enfeebled action of

[1] Kolbe, "Ueber eine neue Darstellungsmethode und einige bemerkenswerk Eigenschaften der Salicylsäure," 'Journ. f. prakt. Chemie,' 1874—1880, Bd. x, S. 89 and 213; Bd. xi, S. 9; Bd. xii, S. 151 and 161; Bd. xiii, S. 106; Bd. xvii, S. 347; Bd. xxi, S. 443; Bd. xxii, S. 112. C. E. Buss, "Ueber die Anwendung der Salicylsäure als Antipyreticum," Doctordissertation, Basle, 1875 (printed in the 'Arch. f. klin. Med.,' Bd. xv, S. 457). Immediately after the publication of this paper an immense number of confirmatory reports appeared in the various medical journals throughout the world.

the heart, considerable fall of temperature, and death from complete paralysis. In one case 22 grammes (330 grains) of sodium salicylate were given, by mistake, to a female patient in six hours. The consequences were violent headache, disturbances of hearing and vision, profuse perspiration, melancholia, mydriasis and divergent squint, hoarseness and difficulty in speaking. The symptoms disappeared in a few days, but returned in a slighter and more transient form after the subcutaneous injection of 0·02 gramme ($\frac{1}{3}$ of a grain) of the acid.[1] The administration of 15 grammes (about 230 minims) of the ethereal oil of *Gaultheria procumbens*, methyl-salicylic ether, produced violent singing in the ears and great drowsiness.[2]

Salicylic acid differs in its action in some respects from quinine. Generally speaking, larger doses of the former are required to produce any effect upon the human subject; it is apt both in healthy individuals and in invalids to induce perspiration, which is often profuse; and it affects the heart more readily than quinine does.

The ANTIZYMOTIC property of salicylic acid is, therapeutically, of importance. This is due, as is the case also with quinine, to its direct effect upon the protoplasm of the organism which sets up the putrefactive or fermentative changes, and does not depend upon its simple presence as a free acid, since other free acids, when present in the same proportion, are far less effective. This specific property of salicylic or ortho-oxybenzoic acid is dependent on the fact that it is a near derivative of carbolic acid; though it is somewhat remarkable that the isomeric compounds, para- and meta-oxybenzoic acid, do not possess the same antizymotic property. Here we are met, as I have previously remarked, by conditions, which, so far, have not been satisfactorily explained.

Salicylic acid also impedes various transformations or decompositions which result from the presence of certain SOLUBLE ferments,—such, for instance, as the decomposition

[1] F. Petersen, "Acute Vergiftung mit Natr. Salicyl. und subcut. Inject. von Acid. Salicyl. bei Erysipel.," 'Deutsche med. Wochenschr.,' 877, S. 13 u. 29.

[2] Hamilton, 'New York Med. Journ.,' 1875, i, p. 602.

of amygdalin by emulsin, and of myronic acid, in black mustard seeds by synaptase. But here also the rule holds good that a larger quantity of salicylic acid than of quinine is required for these purposes. Physiological ferments, such as pepsin and trypsin, may be preserved from decomposition by the addition of a little salicylic acid, and their specific properties are not affected thereby.

Kolbe, judging from the results obtained by quinine, attributed the antipyretic action of salicylic acid to its antizymotic property. Two facts, however, are opposed to this view: first, salicylic acid is unquestionably combined with soda in the circulation; and secondly, sodium salicylate is as strongly antipyretic as the free acid,—although in neutral or alkaline solutions, and consequently in the fluids of the body, it has much less antizymotic power than the acid.

These facts led to a considerable amount of discussion. I believe, however, that I have, by means of experiments, succeeded in solving the apparent contradiction.[1]

Salicylic acid, no doubt, liberates carbonic acid from its compounds; but, if another substance be present—such as ether—in which salicylic acid, but not its sodium salt, is readily soluble, we can reverse the process, and, as you see here, by shaking the mixture up with carbonic acid, separate the salicylic acid from the sodium salt, even if the solution has been previously rendered alkaline by the addition of a little sodium phosphate and carbonate. If we leave the ether to evaporate in a glass vessel, we obtain a residuum of free salicylic acid.

I have carried this experiment a step further, with the following result. The addition of 0·5 per cent. of sodium salicylate to a clear nutritive medium for bacteria cultivation —that is, to a solution of sugar, potassium phosphate and ammonium tartrate, rendered alkaline by a little soda—proved of no value whatever as a preservative, for in a few days the growth of micro-organisms made the solution quite opaque (Fig. A).

[1] C. Binz, "Die Zerlegbarkeit des salicylsauren Natrons," 'Berl. klin. Wochenschr.,' 1876, No. 27; "Die Einwirkung der Kohlensäure auf salicylsaures Natron," 'Arch. f. Path. u. Pharmak.,' 1879, Bd. x, S. 147.

In a second experiment the nutritive solution, with 20 per cent. by volume of carbonic acid added to it, and under a pressure of 360 mm. of mercury, kept clear two days longer, but then decomposed as rapidly as the other.

In a third experiment the solution, with the addition of 0·5 per cent. of sodium salicylate and 20 per cent. by volume of carbonic acid, under the same pressure as in the last, remained absolutely unchanged for more than two years in a warm room, and would undoubtedly have done so longer had it not been desirable to open the flask in order to examine more minutely the condition of the liquid. In other words CARBONIC ACID AT A HIGHER TENSION CONVERTS SODIUM SALICYLATE INTO A POWERFULLY ANTIZYMOTIC AGENT (Fig. B).

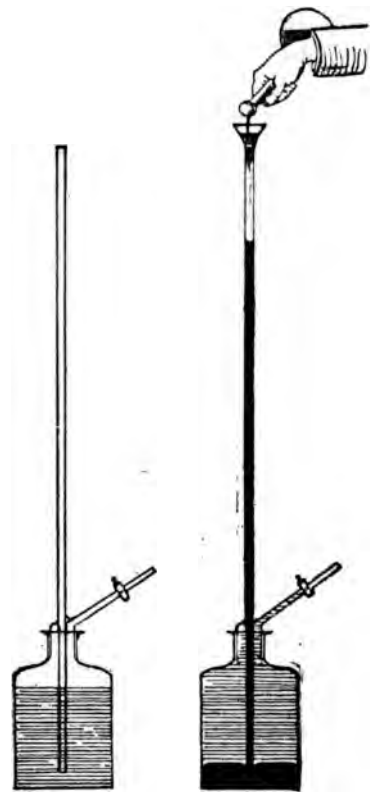


FIG. A. FIG. B.

In the flask A the carbonic acid gas under the ordinary atmospheric pressure rests on the surface of the slightly putrescent liquid, which is saturated with the gas; in B the increased pressure from the mercurial column has caused the liquid to absorb the gas.

There is, moreover, the fact that after giving sodium salicylate to animals, and subsequently suffocating them, free salicylic acid can be extracted from their blood on agitating it with ether, though this cannot be done if the animal has not been asphyxiated.

The amount of carbonic acid found in the blood of asphyxiated animals does not exceed 12·6 per cent.,[1] while in the inflamed tissues of the human subject it amounts to as

[1] Ludwig und Holmgreen, ref. 'Jahresb. d. ges. Med.,' 1865, S. 152.

much as 17·5 per cent.[1] The tension is accordingly lower in the former condition than in the latter. But if with the lower tension the salicylic acid is liberated from the sodium, and thus becomes—as my experiments prove—strongly antizymotic, the change will be produced much more readily under the higher tension. In the inflamed tissues the conditions are very similar to those of my experiment, and we may therefore expect that the action of the sodium salicylate will be the same, namely, to check any zymotic processes arising from morbid irritation.

Sodium salicylate is not, however, as was once supposed, without effect upon protoplasm. If we compare the action of a 1 per cent. solution of sodium salicylate with that of a similar solution of sodium chloride upon motile lymph cells, vigorous paramecia, or upon the liberation of nascent oxygen which results from the action of fresh vegetable protoplasm on guaiacum resin, we perceive in each case that there is diminished activity in that specimen containing the salicylate. This diminished activity, though less marked than that produced by the acid itself, or by some salt of quinine, is nevertheless unmistakable.[2] It may also result from the liberation of the acid by means of other acids, and particularly by carbonic acid at an increased tension.

Let us apply all these observations to the special therapeutic effects produced by salicylic acid. In ACUTE RHEUMATISM it acts almost with the same rapidity and certainty[3] that iodide of potassium does in syphilitic disease of the bones, or quinine in malarial poisoning. Not only does the fever abate in a very short time, but the violent pain and tense swelling of the joints also disappear. Its action in this respect does not depend upon the reduction of the fever, for other antipyretics can lower the temperature without any effect being produced on the swelling and pain. It appears, therefore, that the remedy acts directly upon the special cause which produces the morbid changes in rheumatism.

[1] A. Ewald, 'Arch. f. Anat. u. Physiol.,' 1876, S. 446.

[2] C. Binz, 'Arch. f. exper. Path. u. Pharm.,' 1877, Bd. vii, S. 280.

[3] C. E. Buss, loc. cit., S. 488; Stricker, 'Berl. klin. Wochenschr.,' 1876, Nos. 1 and 2.

As Latham[1] correctly remarks, "So long as the rheumatic poison is circulating in the system, the physiological effect of the remedy—that is the effect it produces in the healthy organism—does not show itself; as it is acting as an antidote, the greater the amount of poison, the larger must be the dose of the remedy; but as soon as the formation of the *materies morbi* is stopped, then the excess of the remedy acts as it would in the healthy organism, and its peculiar physiological effects are developed. It is a very striking illustration of the difference between the therapeutic effect of a remedy and its physiological action."

According to the view above stated, from the sodium salicylate carried in the circulation to the tense and acutely inflamed joint, the free salicylic acid with its antizymotic properties will there be continuously but temporarily liberated, and in this way neutralise the rheumatic poison. At all events, it cannot be maintained that the sodium salicylate circulates in the INFLAMED parts of the body, as a neutral salt undergoing no change there, and having no effect on the part.

My experiments serve also to explain why sodium salicylate unfortunately fails to check rheumatic mischief in the LEFT SIDE OF THE HEART. It meets there with very little carbonic acid—only 2·8 per cent.—and is not subjected to the increased pressure which is exerted in the tense fibrous tissues enveloping the joints. In the heart the circulation is rapid and unimpeded; in the inflamed joints the vessels are compressed, and the blood, overcharged with carbonic acid, flows more slowly through them. In the heart THOSE VERY CONDITIONS ARE WANTING UNDER WHICH SALICYLIC ACID CAN BE LIBERATED BY CARBONIC ACID.

We have rightly abandoned a view formerly advanced on scientific grounds, which attributed the antipyretic action of salicylic acid to a lowering of the activity of the heart and of the respiratory organs. Within certain wide limits, the blood-pressure and respiration are not concerned either

[1] P. W. Latham, "On the Administration of the Salicylates in Acute Rheumatism," 'Medical Magazine,' London, 1895, pp. 246–7. The Croonian Lectures on some points in the Pathology of Rheumatism, &c., Cambridge, 1887, p. 94.

with the degree of metabolism of albumen, or with the amount of tissue oxidation arising in the system. Nor is the profuse sweating, which sometimes accompanies a fall in the temperature, a necessary condition of antipyretic action. Writing to me, A. Ewald says, "I have finished the thermo-electric experiments on the fall of temperature after salicylic acid, the results of which prove that the fall is absolutely identical both in the stomach and in the axilla, and consequently is due to diminished oxidation, and not to increased radiation from the surface." We know, moreover, that a fall of temperature very often occurs without perspiration, and perspiration without a fall of temperature.

Just as quinine not only cures the fever, but also the malarial cachexia which is unaccompanied by fever, so also the continuous use of salicylic acid may cure the apyretic form of chronic rheumatism.[1] The results of experiments with it are as follows:

"The repugnance which some patients have to the remedy can be overcome. Its unpleasant collateral effects become gradually less marked. Sodium salicylate is innocuous, even when taken for years (4 or 5 grammes [60 to 75 grains] being taken for a dose every night). It loses its efficacy if taken for too long a time, and its use must therefore be discontinued occasionally."

Recent as well as chronic pleuritis, unaccompanied by purulent effusion, may be advantageously treated with full doses of sodium salicylate,[2]—5 grammes (75 grains), for instance, being given an adult in twenty-four hours.

An experiment has been carried out on insects which is very instructive.[3] Bees are liable to "foul brood," a highly infectious disease caused by microscopical schizophytes. This fungus develops and spreads in the bees both externally and internally. Larvæ fed on food containing the fungus are affected internally. It affects whole hives, and renders them putrid. No remedy appeared to be of any ser-

[1] B. Brandis, 'Ueber die Behandlund des chronischen Gelenkrheumatismus,' 1882, S. 12—24.

[2] Aufrecht und B. Tetz, 'Therap. Monatshefte,' 1890, S. 323.

[3] C. O. Cech, 'Salicylsäure als Heilmittel der Brutpest der Bienen,' 1877.

vice, but if bees attacked by it are fed with syrup containing about 0·16 per cent. of salicylic acid the disease completely disappears, and the insects recover their usual activity and vigour.

Whilst these arguments and facts point to a direct antizymotic action, it is not to be denied that possibly salicylic acid, like quinine, may in many cases also influence the heat-regulating centre.[1] Both actions may take place simultaneously. The statement that the remedy paralyses the cause which gives rise to the morbid conditions, even though, as in rheumatism, the cause itself remains unknown, is a sufficient explanation of the effect of salicylic acid in rheumatic disorders, and of quinine in malarial fever.

The EXCRETION of salicylic acid seems to take place very quickly and in all directions.[2] On adding perchloride of iron to a solution containing salicylic acid (and it is well previously to acidulate the solution) a reddish-purple colour is produced. This can easily be observed in the urine. In the human subject the urine, after the administration of salicylic acid, has a slight greenish tinge, soon darkens and turns to an olive-green colour, with an iridescent violet edge. This arises from an increase, often considerable, of the substance which when treated with the usual reagents furnishes the indigo blue of urine.[3] Besides this antecedent of indigo we have, in the urine, salicyluric acid,[4] resulting from the combination of salicylic acid with glycocoll, water being eliminated:

$$\underset{\text{(Salicylic acid)}}{C_7H_6O_3} + \underset{\text{(Glycocoll)}}{C_2H_3(NH_2)O_2} - H_2O = \underset{\text{(Salicyluric acid)}}{C_9H_9NO_4}.$$

Part of the salicylic acid passes off unchanged, which is probably the reason why urine under these conditions does not readily decompose. Salicylic acid, unlike its two isomers, para-oxybenzoic acid and meta-oxybenzoic acid, and unlike

[1] Zuntz, 'Verhandl. d. Congr. f. innere Med.,' Wiesbaden, 1885, S. 184.

[2] T. Pauli, "Der Uebergang der Salicylsäure in die Milch der Wöchnerinnen," Doctordiss., Berlin, 1879.

[3] S. Wolffberg, 'Arch. f. klin. Med.,' 1875, Bd. xv, S. 403.

[4] Bertagnini, 'Ann. d. Chemie,' 1856, Bd. xcvii, S. 248.

carbolic acid, does not form double compounds with sulphuric acid.[1]

At the present moment these matters have only a chemico-physiological interest for us. Of greater importance, from our point of view, is the influence of salicylic acid upon METABOLISM. Excessive doses increase the albuminous waste in animals and human beings, as measured by the amount of sulphur and nitrogen in the urine. Doses of 0·25 to 2·50 grammes (3¾ to 38 grains) of sodium salicylate produce no effect on healthy human subjects; doses of 5 grammes (75 grains) reduce the total daily excretion of nitrogen in the urine on an average from 19·3 to 17·4 grammes (290 to 261 grains).[2]

In the case of two diabetic patients,[3] the daily administration of 5 to 10 grammes (75 to 150 grains) of sodium salicylate reduced the average daily excretion of urea, estimated on six consecutive days, from 45·3 to 32·8 grammes (680 to 480 grains), causing a corresponding increase, during the week, of several pounds in the weight of the patient, which, however, were lost again when the remedy was discontinued. In one case the excretion of sugar diminished considerably—from about 369 grammes to 185 and 154 grammes in the twenty-four hours. This last effect had previously been noted.[4] In a third case the remedy produced no definite effect either upon the excretion of nitrogen or of sugar.

A noticeable increase in the excretion of URIC ACID is often observed under the most varied conditions after the administration of sodium salicylate. This occurred in the diabetic patients above mentioned, the excretion of uric acid increasing to five times its normal amount. As yet it is not determined whether this arises from its formation in larger quantities, or from the more rapid excretion of the acid already present in the body, or from its oxidation into urea being diminished. The secretion of urine is considerably

[1] E. Baumgarten u. E. Herter, 'Zeitschr. f. physiol. Chemie,' 1878, Bd. i, S. 253.

[2] E. Salomé, 'Wiener med. Jahrbücher,' 1885, S. 463.

[3] P. Fürbringer, 'Arch. f. klin. Med.,' 1878, Bd. xxi, S. 476.

[4] W. Ebstein, 'Berl. klin. Wochenschr.,' 1876, No. 24.

increased, especially in cases of pleurisy, by salicylic acid;[1] so also is the secretion of bile.[2]

A curious effect on the bile has been observed to follow the administration to dogs of a moderate dose of sodium salicylate.[3] The thick and viscid bile becomes liquid, and almost as transparent as water, and the green colour which it acquires on standing is more slowly developed. There is a diminution of the solids by more than one half. Good results seem to have been obtained therapeutically in biliary colic from the administration of moderate doses of this remedy.[4]

Many unpleasant COLLATERAL EFFECTS are produced by salicylic acid, among which its enfeebling effect on the action of the heart is most important. In febrile disorders salicylic acid is very apt to accelerate the pulse and diminish its force, and therefore should not be employed when the pulse is already very rapid, or when the heart's action appears to be enfeebled. Collapse may be produced by a dose of not more than 5 grammes (75 grains).[5]

Albuminuria, suppression of urine, and œdema of the legs[6] have resulted from a dose no larger than 4 grammes (60 grains). The symptoms passed off when the remedy was discontinued, and returned when the dose was repeated. They are, therefore, not dangerous symptoms, and they do not occur very frequently. There is sometimes also a simultaneous rise of temperature; a rise as high as 40° C. (104° F.) has been noted under these circumstances.

At all events, in acute rheumatism complicated with albuminuria, the use of the drug is contra-indicated, for Noel

[1] Huber, 'Arch. f. klin. Med.,' 1887, Bd. xli, S. 129.

[2] S. Rosenberg, 'Berl. klin. Wochenschr.,' 1889, S. 1070.

[3] W. Lewaschew, 'Zeitschr. f. klin. Med.,' 1884, Bd. viii, S. 67; 'Arch. f. klin. Med.,' 1884, Bd. xxxv, S. 122; 'Arch. f. pathol. Anat.,' 1885, Bd. ci, S. 430.

[4] Stiller, ref. 'Therap. Monatshefte,' 1890, S. 139. Doses of 0·5 gramme (7½ grains) were given four times a day. The remedy was generally combined with extract of belladonna, which makes it difficult to estimate its true value. G. See, of Paris; Fürbringer, 'Verhandl. d. Congr. f. innere Med.,' 1891, S. 62.

[5] Goltdammer, 'Berl. klin. Wochenschr.,' 1876, S. 47.

[6] Lürman, ibid., 1876, S. 477; Baruch, ibid., 1883, S. 505.

Paton's[1] experiments show that it "has really an irritating action on the kidneys."

In some individuals it gives rise to hæmorrhage from the mucous membranes.[2] In females where this tendency exists the use of the remedy may occasion frequent or excessive menstruation, or if the patient is pregnant may cause miscarriage or premature birth.

These facts, therefore, must be borne in mind when prescribing salicylic acid for females. It is asserted, especially by French physicians, that one of the direct effects of salicylic acid is to cause abortion—a view which seems to be supported from experiments on pregnant rabbits.[3] This is a matter which requires further careful investigation.

In some individuals cutaneous eruptions of all kinds are developed by the use of salicylic acid or sodium salicylate, and may be accompanied by rigors and a febrile temperature, the latter rising as high as 40·2° C. (104·4° F.).[4] Inflammation of the internal ear may be set up, as sometimes happens after the administration of quinine. In one case 30 grammes (450 grains) were taken in the course of fourteen days, in doses of 1 gramme (15 grains) at a time. Tinnitus aurium and deafness ensued; the former soon passed off, but the latter was permanent. Mental derangement has also followed the continued administration of large doses of sodium salicylate.[5] It is evident, therefore, that in all cases great care must be exercised in the administration of this remedy, although, as a rule, it is readily tolerated and acts beneficially.

A reference must not be omitted to the solvent action of salicylic acid upon corns, especially when applied as a plaster or mixed with collodion. It is distinguished from all other preparations hitherto known and used for this purpose in that, even when applied in a concentrated form,

[1] Noel Paton, 'Journ. of Anat. and Physiol.,' 1886, January, p. 25.

[2] Pullmann, 'Berl. klin. Wochenschr.,' 1889, S. 604; B. Schuchardt, 'Corresp.-Blätter d. allgem. ärztl. Ver. von Thüringen,' 1886, No. 7; J. Wacker, 'Cbl. f. Gynäkol.,' 1889, S. 685; Linhart, ibid., 1890, S. 488.

[3] C. Binz, "Die Wirkung der Salicylsäure auf die Gebärmutter," 'Berl. klin. Wochenschr.,' 1893, No. 41.

[4] Erb, 'Berl. klin. Wochenschr.,' 1884, No. 29.

[5] Obersteiner, 'Wiener Klinik,' 1886, S. 42.

its action is limited to the corneous layer. It does not affect the stratum Malpighii, and consequently does not, as corrosive sublimate does, produce blisters or vesicles, nor is its action of an ordinary caustic nature; the corneous layer acted upon by salicylic acid simply peels off, after some days, as a soft, bleached, coherent membrane.[1]

The following are the officinal preparations:

ACIDUM SALICYLICUM, salicylic acid; white, odourless, acicular crystals, light and easily diffused; taste at first sweetish and then acid; soluble in 500 parts of cold water, readily soluble in alcohol and ether; fusing at about 155° C. (311° F.), and below 200° C. (392° F.) volatilising without decomposition, but if rapidly heated volatilising with an odour of carbolic acid. The aqueous solution gives a reddish-violet colour with solution of perchloride of iron. This preparation disagrees with the stomach, causing irritation and indigestion. It has consequently been almost entirely discarded in favour of the following.

NATRIUM SALICYLICUM, sodium salicylate. This consists of small, white, crystalline scales, odourless, anhydrous, and having a sweetish saline taste, soluble in 0·9 part of water and in 6 parts of alcohol. Perchloride of iron colours a concentrated solution reddish brown, and a dilute solution violet. A concentrated aqueous solution has a slightly acid reaction, and after standing for some time should develop only a faint red colour, a deep red colour indicating the presence of carbolic acid. The dose for adults varies from 0·5 to 5 grammes (7½ to 75 grains).

Sodium salicylate is most readily tolerated by the stomach when given in conjunction with from 0·5 to 1 gramme (7½ to 15 grains) of bicarbonate of soda, as the mild alkali prevents the precipitation of the comparatively insoluble salicylic acid by the hydrochloric acid. If given without this addition sodium salicylate is apt to induce dyspepsia. When the remedy cannot be taken by the mouth, without discomfort, it may be given in the form of an enema, the rectum being previously washed out with a moderate quantity of water. It is readily absorbed in this way, and a somewhat larger dose may be given.

[1] P. G. Unna, 'Aerztl. Vereinsbl.,' 1885, S. 194.

Pulvis Salicylicus cum Talco, salicylic dusting powder, is only used externally. It consists of three parts of the acid, ten parts of wheaten starch, and eighty-seven parts of talc (a magnesium silicate, the composition of which is $3MgSiO_3 + H_3SiO_3$), and is a fine white, dry powder. Where there is a tendency to excessive perspiration of the feet, as much of this powder as will lie on the point of a knife, sprinkled inside the stockings, will diminish the secretion and prevent its decomposition. The starch merely serves to retain the powder in the stockings. Talc itself is also used as a dusting powder in the treatment of skin diseases. It is insoluble in the animal fluids.

Sebum Salicylatum, salicylic ointment, is a white substance made by melting ninety-eight parts of mutton suet with two of salicylic acid.

Salicylic acid was employed medicinally long before it was actually discovered. Even among the ancients [1] the bitter taste of the willow bark led to a decoction of it being employed medicinally. The practice continued all through the Middle Ages,[2] and the estimation in which it has frequently been held in subsequent times, may be inferred from the title [3] of one of the numerous treatises which were written upon it.

When the first Napoleon declared the whole Continent to be in a state of blockade, the price of cinchona bark rose very high, and willow bark was largely used as a substitute. Decoctions of it cured or relieved the milder forms of fever.

The extraction, about the year 1830, of the bitter prin-

[1] Dioscorides, lib. i, cap. 135; Cl. Galenus, 'Opera omnia,' ed. Kühn, lib. x, p. 891, and in many subsequent passages.

[2] In the 'Schola Salernitana' (cap. 72) it is thus fancifully referred to:

"Auribus infusus vermes succus necat ejus.
Cortex verrucas in aceto cocta resolvit.
Hujus flos sumptus in aqua frigescere cogit
Instinctus Veneris cunctos acres stimulantes,
Et sic desiccat, ut nulla creatio fiat."

[3] S. James, 'Observations on the Bark of a particular species of Willow, showing its superiority to the Peruvian, and its singular efficacy in the cure of ague, fluor albus, abscesses, hæmorrhages, &c., with cases,' London, 1792.

ciple which exists in large quantities in some species of willow (and also in the buds, &c., of the poplar) led to fresh experiments. SALICIN, a glucoside having the formula $C_{13}H_{18}O_7$, was found to act as an antipyretic, though only to a slight and uncertain extent. It was discarded, as a remedy, until attention was again called to it in 1876 simultaneously by Maclagan[1] and Senator.[2]

This was not unnatural, for chemical research had in the meantime demonstrated that, under the action of the saliva and other bodies, salicin takes up a molecule of water, and is decomposed into saligenin and glucose:

$$\underset{\text{Salicin.}}{C_{13}H_{18}O_7} + H_2O = \underset{\text{Glucose.}}{C_6H_{12}O_6} + \underset{\text{Saligenin.}}{C_7H_8O_2}.$$

The saligenin is oxidised in the system into salicylic acid,[3] and appears as such in the urine after the administration of salicin.

$$\underset{\text{Saligenin.}}{C_7H_8O_2} + 2O = H_2O + \underset{\text{Salicylic acid.}}{C_7H_6O_3}.$$

One portion of the salicin undergoes both these changes in the body, another portion is either undecomposed or is converted into saligenin and salicylous acid, $C_7H_6O_2$ (salicylic aldehyde $C_6H_4.OH.COH$).[4]

Salicin in doses of from 2 to 10 grammes lowers the temperature in febrile disorders quite as effectually as salicylic acid; in rheumatism its action is equally satisfactory, and in ague equally uncertain. Its price, and the existence of the easily obtained salicylic acid, have, however, prevented salicin from being generally employed in medical practice, notwithstanding Senator's statements that it can be taken for a longer time than salicylic acid without giving rise to impaired digestion, profuse perspiration, or collapse, that its effects are more gradual but more lasting, and that it is particularly useful in chronic and painful affections of the joints. It is, nevertheless, interesting to observe that by the chemical and therapeutic knowledge of the present day it is proved that the ancient followers of the medical art judged

[1] Maclagan, 'Lancet,' 1876, March 4 and 11.

[2] Senator, 'Cbl. f. d. med. Wissensch.,' 1876, S. 241; 'Berl. klin. Wochenschrift,' 1877, No. 14.

[3] Nencki, 'Arch. f. Anat. u. Physiol.,' 1870, S. 399.

[4] Marmé, 'Nachr. d. Göttinger, Ges. d. Wiss.,' 1878, S. 229.

rightly in regarding willow bark as a useful remedy in febrile disorders.

The salicylous acid, above referred to, has no antipyretic action, but in large doses it stimulates the heart and spinal cord, and by its effect on the latter may give rise to convulsions.[1] When once formed in the system it is excreted as such in the urine without being further oxidised into salicylic acid. Salicin itself, unless transformed into salicylic acid, does not prevent fermentation or putrefaction.

It has recently been discovered that the flowering plant HERBA VIOLÆ TRICOLORIS, or heart's-ease, which grows wild in Europe, contains salicylic acid. It was formerly employed both externally and internally in the treatment of eczematous and impetiginous eruptions. The dried plant has a very faint, somewhat pleasant odour, but is without any characteristic taste. In 1879 Mandelin of Dorpat detected the presence of salicylic acid, and a considerable amount of magnesium tartrate, in this plant.

SALOLUM is salicyl-phenyl-ether, $C_6H_4.OH.COOC_6H_3$, a white crystalline powder which has a faintly aromatic odour and taste; it is scarcely soluble in water, but dissolves readily in alcohol and ether, and is used both externally and internally for the same purposes as its five constituents. The average dose is 0·5 gramme (7½ grains) several times a day. Its absorption takes place in the intestine. Like carbolic acid, it renders the urine of an olive-green or greenish-black colour. The antiseptic properties of salol are not brought into play until it reaches the small intestine, where it is decomposed by the alkaline secretions of the part into salicylic and carbolic acids. It is probably on this account that it is beneficially employed in the treatment of such parasitic disorders as have their seat in the intestine.[2]

[1] S. Ringer ('Journ. of Anat. and Physiol.,' vol. xi, p. 589) states that he has given to a boy of ten years of age doses of salicin amounting in all to 180 grains (= 12 grammes) a day without any disturbance of the general condition beyond some increased frequency of the pulse and slight deafness. The treatment, which began with 80 grains, lasted twenty-four days.

[2] Sahli, 'Corresp.-Bl. f. Schweizer Aerzte,' 1888, Nos. 12 und 13; 'Therap. Monatshefte,' 1887, S. 333; N. Wolkowitsch, "Ueber der therap. Wert des Salols bei der Cholera-Diarrhöe," ibid., 1894, S. 456.

Salol was first prepared by Nencki of Berne in 1883, and is officinal in Germany. As it is not soluble in the stomach it may be used as a coating for pills, the action of which is to be delayed until they reach the small intestine.

The discovery of the antipyretic properties of salicylic acid led to an active search, among the various aromatic compounds which modern chemistry has produced, for substances of similar properties. One of the first to be investigated was BENZOIC ACID, $C_6H_5.COOH$, which was formerly officinal, and is prepared from benzoin by sublimation. It consists of laminated or acicular crystals, white at first and then turning yellow or brownish yellow, with a silky lustre and an agreeable aromatic odour resembling that of benzoin. It requires 400 parts of cold water for solution, but is readily soluble in rectified spirit, ether, or chloroform, and volatilises in steam. BENZOIN is found in many plants and vegetable preparations; the officinal form is the resin from *Styrax benzoin*, a tree indigenous in Sumatra and Siam. The resin occurs as greyish-brown lumps, white inside, which give off an aromatic odour when heated, and are almost entirely soluble in alcohol, the solution having an acid reaction.

Benzoic acid can also be prepared by oxidising oil of bitter almonds, $C_6H_5.COH$. It is also prepared by boiling hippuric acid with hydrochloric acid, when by hydrolysis hippuric acid is resolved into benzoic acid and glycocoll. Another source is the putrescent urine of horses or cattle (the benzoic acid *ex urina* of commerce). In the system benzoic acid combines with glycocoll, and H_2O being eliminated, it appears in the urine as hippuric acid:

$$\underset{\text{Benzoic acid.}}{C_7H_6O_2} + \underset{\text{Glycocoll.}}{C_2H_3(NH_2)O_2} = H_2O + \underset{\text{Hippuric acid.}}{C_9H_9NO_3}.$$

Both gum benzoin and benzoic acid, but especially the latter, have been employed in order to promote the expectoration of mucus when this was accumulating in the bronchial

tubes; to render the urine acid,[1] and so prevent or dissolve concretions in the bladder which may result from alkalinity of the urine; and as an external application in various cutaneous disorders. For the first-mentioned purpose especially, benzoic acid was and still is, frequently used, though its employment is not based upon any scientific facts. It was, moreover, discovered that benzoic acid is more destructive in its action on the lowest forms of organic life[2] than carbolic acid, and that it has a stronger antiseptic action than salicylic acid.[3]

The correctness of these observations was confirmed by a series of exhaustive experiments,[4] and finally Senator[5] proved that benzoic acid also possesses an antipyretic action, which is particularly marked in acute articular rheumatism. He also maintained that its use is preferable to that of salicylic acid, inasmuch as it does not give rise to irritation of the stomach, kidneys, and bladder, which is an occasional effect of salicylic acid, nor to tinnitus aurium and perspiration, effects which are almost invariably produced by the latter. He also states that some cases, in which salicylic acid had proved ineffective, were cured or ameliorated by benzoic acid, though much less quickly than is usually the case with salicylic acid.

Benzoic acid has, consequently, been very largely employed, and its sodium salt has been also included in the pharmacopœia.

The disadvantage attending this mode of treatment is, that occasionally a single dose of 6 or 8 grammes (90 to 120 grains) of the acid or salt, sets up all kinds of disturbed action in the stomach and intestines.

The following[6] is an account of the poisonous effects produced by the drug. A well-built man, suffering from tuber-

1 G. Kerner, 'Arch. f. wissensch. Heilkunde,' Gottingen, 1858, Bd. iii, S. 616.

2 P. Dougall, 'Med. Times and Gaz.,' 1872, i, p. 495.

3 Salkowski, 'Berl. klin. Wochenschr.,' 1875, S. 297.

4 L. Bucholtz, 'Arch. f. exper. Path. u. Pharmak.,' 1875, Bd. iv, S. 37 G. Brown, ibid., 1877, Bd. viii, S. 141; Schüler, ibid., 1879, Bd. xi, S. 84.

5 Senator, 'Zeitschr. f. klin. Med.,' 1879, Bd. i, S. 243.

6 Fritsche, 'Berl. klin. Wochenschr.,' 1879, S. 760.

culosis, was in the habit of inhaling 2·5 grammes (38 grains) of benzoic acid three or four times a day, and appeared to derive great benefit therefrom; the pain in the throat and the cough entirely disappeared, while the appetite and the general condition of the patient improved. After three weeks of this treatment the dose was doubled. The results were loss of appetite, and a return of the cough and pain in the throat. Contrary to the advice given to the patient, he persisted in using the stronger solution. The cough became more troublesome, and vomiting, diarrhœa, strangury, conjunctivitis, and extreme general debility were set up, which lasted for several days. The skin and urine smelt of benzoin, or rather of the aromatic substances allied to the officinal acid, as when chemically pure the latter is inodorous.

An ovarian cyst was evacuated and afterwards washed out with a solution containing 100 grammes (about 3½ oz.) of sodium benzoate. This was followed thirty hours afterwards by delirium and stupor, profuse perspiration, tremulousness of the hands, and a weak, running pulse. The urine contained a considerable amount of hippuric, but no benzoic acid.[1] After the administration of large doses of sodium benzoate the urine contains a substance which is capable of reducing cuprous oxide, but which, nevertheless, is not a glucose.[2]

Such isolated examples, however, of the unpleasant collateral effects produced by benzoic acid, do not detract from the value of sodium benzoate as being, in many cases, a useful substitute for sodium salicylate. The dose is from 8 to 10 grammes (120 to 150 grains) in the twenty-four hours.

Tinctura Benzoes, tincture of benzoin, is a solution of one part of the resin in five parts of rectified spirit. It is reddish yellow in colour, with the odour of benzoin, and forms, when water is added, a mixture with a milk-like appearance and a

[1] v. Mörner, 'Cbl. f. d. med. Wiss.,' 1888, No. 29.

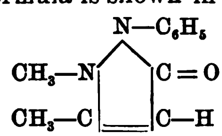
[2] With regard to the action of this group of remedies upon the metabolism of albumen (in dogs) see M. Kumagawa, 'Arch. f. pathol. Anat.,' 1888, Bd. cxiii, S. 134, which also contains the bibliography of the subject. See also the somewhat divergent results of Horbaczewski's experiments in the 'Wiener med. Jahrb.,' 1885, S. 464.

strong acid reaction. It is chiefly used externally in cutaneous disorders.

Adeps Benzoatus, benzoated lard, is hog's lard to which, when melted, 1 per cent. of sublimated benzoic acid has been added.

The success of salicylic acid as a therapeutic agent, together with the various attempts to synthesise quinine—a remedy which was so costly only a few years ago,—and the marvellous progress which has been made in synthetic chemistry soon led to the introduction of other remedies of an allied character. I pass over those which have already fallen into oblivion, and which turned out, in spite of some good results at first, to be neither useful nor free from danger, and proceed to discuss—in the order of their introduction into therapeutics—four later antipyretic remedies which have been included in the German Pharmacopœia.

Antipyrinum, antipyrin, $C_{11}H_{12}N_2O$. Obtained by the condensation of phenyl-hydrazin, $C_6H_5.NH.NH_2$ (a derivative of aniline, $C_6H_5NH_2$, and nitric acid), with aceto-acetic ether.[1] It crystallises in colourless plates having a scarcely perceptible odour and a slightly bitter taste. The crystals are soluble in less than one part of water, in one part of rectified spirit or chloroform, and in fifty parts of ether. The aqueous solution has a neutral reaction, but antipyrin is nevertheless a base, and forms salts by directly combining with acids. Its constitutional formula is shown in the following diagram:



If given in febrile conditions to adults, in doses of 1 gramme (15 grains), and the dose repeated two or three times, it lowers the temperature,[2] and also relieves the symptoms dependent on the pyrexia, namely, the frequency of

[1] Acetic ether in which one of the H atoms of the methyl group is replaced by acetyl, C_2H_3O. The molecular constitution of aceto-acetic ether may also be represented thus:

$$\underset{\text{Acetic ether.}}{C_2H_5.C_2H_3O_2} + \underset{\text{Acetic acid.}}{HC_2H_3.O_2} - \underset{\text{Water.}}{H_2O} = \underset{\text{Aceto-acetic ether.}}{C_6H_{10}O_3}$$

[2] Filehne, 'Zeitschr. f. klin. Med.,' 1884, Bd. vii, S. 641.

the pulse and respiration, the dry tongue, general discomfort, and delirium. The fall of temperature is generally accompanied by profuse perspiration, but does not result from the latter, as the temperature falls even if the action of the skin is prevented by the administration of 0·001 gramme ($\frac{1}{60}$ of a grain) of atropine, or 0·01 gramme ($\frac{1}{6}$ of a grain) of agaricin.[1] Authorities are not yet agreed as to the way in which the fall of temperature is brought about. The amount of heat given off from the body is increased by the dilatation of the cutaneous arteries; but the amount produced is also decreased, as is apparent from the diminished excretion of nitrogen in the urine, and from the fact that antipyrin lowers the blood-heat of HUMAN BEINGS[2] even in a vapour-bath at 42·5° C. (108·5° F.). Where there is no fever, larger doses are required to reduce the temperature than in the febrile state. It affects the brain less than quinine, and the heart less than salicylic acid. Vomiting, chilliness, impaired respiration, and, more especially, marked cutaneous eruptions,[3] accompanied in some cases with a rise of temperature, have often been noted as undesirable COLLATERAL EFFECTS of even moderate doses. Results of this kind, sometimes even of an alarming character,[4] have been frequently reported in the medical journals of the last few years.

Antipyrin is employed in various febrile conditions. How far, if at all, it affects the cause which produces the rise of temperature we do not know. Like salicylic acid, it has proved very efficacious in acute articular rheumatism, but it produces little effect in malarial disorders. If given in the earliest stage of a simple feverish cold, it may check its further development. It has also proved of service in neuralgia, administered either internally or as a subcutaneous

[1] C. v. Noorden, 'Berl. klin. Wochenschr.,' 1884, No. 32.

[2] C. Engel und Fr. Müller, in Gerhardt's 'Mitteil. a. d. Klin. zu Würzburg,' 1885, Bd. ii, S. 93 und 149.

[3] Doutrelepont, 'Niederrhein. Ges. f. N. u. Heilk.,' 1889, November 18th.

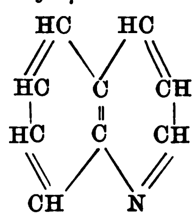
[4] Fr. Tuczek, severe antipyrin poisoning (antipyrin epilepsy) in a healthy boy of four years old suffering from whooping-cough after taking 0·4 gramme (6 grains) of antipyrin three times a day for three weeks.

injection of 0·25 to 0·5 gramme in 1 c.c. (4 to 8 grains in 15 drops) of water, in the region of the pain.[1] In whooping-cough it mitigates the violence of the attacks for a time, without, however, shortening the duration of the illness.

On adding perchloride of iron to an aqueous solution of antipyrin a dark red colour is produced, and the same effect is produced by this reagent upon the urine of patients who have taken the remedy.

Antipyrin should not be prescribed in conjunction with other drugs, as it is very readily acted upon by them, and is either itself decomposed, or it induces chemical change in the substance with which it is brought in contact. If, for instance, it is mixed with moist calomel, a certain amount of the latter is converted into corrosive sublimate.

THALLINUM SULPHURICUM, thallin sulphate. Thallin is a basic substance having the formula $C_{10}H_{13}NO$, and is a derivative of chinoline, C_9H_7N,—



Chinoline.

its actual composition being tetra-hydro-para-methyl-oxy-chinoline. The sulphate is a white or yellowish-white crystalline powder, having an odour somewhat similar to coumarin, and a subacid saline taste; it is soluble in 7 parts of water, and in about 100 parts of rectified spirit, but is less soluble in chloroform, and almost insoluble in ether. The aqueous solution has an acid reaction.

In doses of from 0·1 to 0·5 gramme (1½ to 7½ grains) it perceptibly lowers the temperature of adults in fever; a fall to 32·5° C. (90·5° F.) has been observed[2] after a dose of 1

[1] H. Immermann, 'Deutsche. med. Wochenschr.,' 1886, No. 41; E. Unger, 'Cbl. f. klin. Med.,' 1886, No. 45; F. Merkel, 'Münch. med. Wochenschr.,' 1888, No. 33.

[2] v. Jaksch, 'Verhandlungen d. med. Congresses,' Wiesbaden, 1885, S. 141; C. Alexander, 'Cbl. f. klin. Med.,' 1885, S. 89.

gramme (15 grains). It usually causes profuse perspiration, but unless the dose is excessive it produces no other unpleasant effects; it is asserted more particularly, that it does not give rise either to gastric disturbance or to cutaneous eruptions. It is contra-indicated in cases of heart disease or nephritis. Small and repeated doses of thallin, 0·05 gramme (¾ of a grain), appear to have an almost specific effect in typhoid fever;[1] in malarial disease it produces no beneficial effect. The German Pharmacopœia gives 0·5 gramme (7½ grains) as the maximum single dose, and 1·5 grammes (22 grains) as the largest amount to be administered in twenty-four hours.

Even in a solution of 1 in 1000, thallin sulphate prevents the development on sterilised gelatine[2] of putrefactive germs, and also of gonococci.[3] Antipyrin also possesses antiseptic properties.

The addition of a minute quantity of perchloride of iron to an aqueous solution of thallin develops a bright green colour (whence the name thallin) which subsequently becomes brown. This test produces the same effect also in the urine of patients who have taken thallin.

ACETANILIDUM, acetanilide, antifebrin, $C_6H_5NH.C_2H_3O$. Bright, colourless crystalline flakes, odourless, having a faint, pungent taste, and dissolving in 194 parts of water, or 3·5 rectified spirit. The reaction of both solutions is neutral. It is prepared from acetic acid and aniline, $C_6H_5.NH_2$, and its chemical properties have been well known since its first production by Gerhardt in 1852.

The greater part of what has been said of antipyrin applies equally to antifebrin, both as to the certainty of its action in reducing the temperature,[4] and consequently improving the general condition of the patient, and also as to its effect in curing or relieving neuralgic pain. The antipyretic effect commences generally about an hour and a half

[1] Ehrlich, 'Deutsche med. Wochenschr.,' 1886, Nos. 48 and 50.

[2] Hugo Schulz, 'Cbl. f. d. Med. Wiss.,' 1886, No. 7.

[3] E. Kreis und Goll, 'Corresp.-Bl. für Schweizer Aerzte,' 1887, No. 1.

[4] A. Cahn und P. Hepp, 'Centralb. f. klin. Med.,' 1887, S. 561; Lépine, 'Lyon Médical,' 1888, No. 44.

after the dose has been taken, varying, however, according to the amount of the latter. Perspiration, vomiting, rigors, cyanosis, and collapse are reported as having very frequently followed the use[1] of antifebrin, and in one case after a single dose of 4 grammes (60 grains) the patient became unconscious: generally these unpleasant symptoms are of a transitory character. The cyanosis seems to result partly from a contraction of the arteries, which forces the blood into the veins and distends them, and partly from the formation of methæmoglobin. On the other hand, one case has been reported[2] of a young man who swallowed 30 grammes (450 grains) in one dose; he was seriously affected thereby, but in four days he entirely recovered.

Acetanilide possesses an advantage over antipyrin in being less expensive. The medium dose for adults is 0·25 gramme (4 grains) in powder or pills; the maximum dose is, according to the German Pharmacopœia, 0·5 gramme ($7\frac{1}{2}$ grains).

PHENACETINUM, phenacetin, $C_6H_4NH.C_2H_3O.OC_2H_5$, is the ethyl ether of acetamido-phenol, that is, of acetanilide, one atom of H in the latter being replaced by the molecule OC_2H_5. It consists of shining, colourless laminar crystals, without odour or taste, which are soluble in 1400 parts of water, or 20 of rectified spirit, the solutions having a neutral reaction.

It acts well as an antipyretic, lowering the temperature as much as 2·5° C. (4·5° F.) in a few hours, and at the same time lessening the subjective discomfort.[3] Like antipyrin and acetanilide, it is a nervous sedative;[4] but, on the other hand, like them, if given in too large doses it produces

[1] Kronecker, 'Therap. Monatshefte,' 1888, S. 426; C. S. Freund, 'Deutsche med. Wochenschr.,' 1888, No. 41.

[2] A. Hartge, 'Petersburger med. Wochenschr.,' 1890, S. 69; A. Favrat, "Das Antifebrin in refracta dosi beim Typhus abdominalis, und beim Fieber der Phthisiker," 'Arch. f. klin. Med.,' 1890, Bd. xlvi, S. 511. From the Berne clinic.

[3] Hinsberg und Kast, 'Cbl. f. d. med. Wiss.,' 1887, S. 145; Kobler, 'Wien. med. Wochenschr.,' 1887, No. 26; Lépine, 'Semaine méd.,' 1887, December 21st.

[4] Rumpf, 'Berl. klin. Wochenschr.,' 1888, No. 23.

poisonous symptoms. The medium dose for adults is 0·5 gramme (7½ grains) in powder or pills; 1 gramme (15 grains) is the maximum dose.

Hitherto, among the antipyretic remedies, phenacetin seems to have produced fewer unpleasant and dangerous results, when given in rather large doses, than the others; antipyrin comes next, and then antifebrin. Phenacetin is a less expensive drug than antipyrin.

Von Liebermeister gives an admirable summary of the value and importance of antipyretic remedies in essentially the following terms:[1]

Of all possible methods of combating disease PROPHYLAXIS takes the first place. Next in order is the SPECIFIC PLAN OF TREATMENT, which aims at destroying the actual cause of the disease after it has gained an inroad into the organism, or else to limit its action; the use of quinine in ague, for example, or mercury in syphilis, or salicylic acid in acute articular rheumatism, renders further treatment in many cases superfluous. But there are still numerous disorders against which prophylactic treatment has proved insufficient, and for which as yet there it no specific remedy. Even in such a case we can do much; we can endeavour to steer the course of the disease, and keep the patient alive. The disease will run its course, whatever we do; but we can help to maintain the patient's strength and power of resistance, and we may be able so far to control the symptoms which are indicative of danger, that the danger is obviated. This is the expectant or symptomatic method, and is that which is adopted in by far the greater number of cases in ordinary practice, and which so often saves the life of the patient. Among those symptoms of disease which are indicative of danger, febrile temperature must in many cases be included, and the use of antipyretics then becomes a part of the symptomatic method of treatment. The most complete decline of temperature is of no use unless the general condition of the patient is thereby improved; but all those objections which have been raised against antipyretics are of little account if, under the

[1] v. Liebermeister, 'Verhandl. d. Congr. f. innere Med. Wiesbaden,' 1885, S. 182.

action of the remedy, we find that the general condition of the patient is substantially improved.[1]

[1] v. Ziemssen, 'Antipyrese und antipyretische Heilmittel,' 1887; R. Pott, 'Therap. Monatshefte,' 1888, S. 489 und 539; R. Lépine, 'Arch. de méd. expér.,' 1889, p. 45.

In the 'Verhandl. d. Congr. f. innere Med. Wiesbaden,' 1896, pp. 57 to 75, will be found a detailed report on our present knowledge of the action of the more important antipyretics, which was drawn up by me at the request of the Congress and laid before the meeting.

XXV.

Hydrocyanic acid—Its general and special effects as a poison—Its action on the lowest organisms, on ferments, and on the red blood-corpuscles—Gaseous interchange—Officinal preparations—Treatment of hydrocyanic poisoning—Cyanogen gas—Potassium ferrocyanide.

We now pass to the consideration of the officinal acids. Therapeutically they are most nearly allied to the antipyretics, and the most important among them, though the weakest of all as regards its acid character, is hydrocyanic acid, which is officinal as Aqua Amygdalarum Amararum, bitter almond water. Though it has certainly fallen more and more into disuse, I nevertheless think a detailed discussion of its action will be instructive, as it is one of the drugs which have been most fully studied. It is the strongest poison we have, and in the form of potassium cyanide frequently produces poisonous results.

We will first discuss the chemically pure hydrocyanic acid, HCN, the aqueous solution of which is prepared from a metallic cyanide, by acting on it with a mineral acid and allowing it to distil over into a receiver containing water. The celebrated K. W. Scheele, of Stralsund, who discovered it in 1782, was not aware of its poisonous quality; the chemist Schrader,[1] of Berlin, first referred to this in 1803 as follows:

"As this distilled water (obtained from bitter almonds and cherry laurel) acted in so many ways like distilled hydrocyanic acid (from ferrocyanide of potassium and sulphuric acid), I was curious to see whether hydrocyanic acid also possessed

[1] Schrader, 'Journal der Pharmacie,' Leipzig, 1803, Bd. xi, S. 262 (letter to the editor, J. B. Trommsdorff).

the property, which this water has, of destroying animal life. I therefore gave a few drops of the acid to a sparrow, which was instantly rendered unconscious. The same effect was produced when I held the bird for a little while over the mouth of a bottle containing the acid. Thus in the preparation of Prussian blue, a substance is produced scientifically, similar to that which Nature herself prepares in the organic world."

In the course of this investigation Schrader also discovered—a fact previously unknown—that the water of bitter almonds, and of cherry laurel, contains true hydrocyanic acid. This discovery led to an uninterrupted series of investigations on the subject, which have continued even to the present day.[1]

I place on the table a rabbit weighing 1500 grains, perfectly free, as to fasten it down would interfere with the experiment, and is also quite unnecessary. I inject 0·01 of ordinary cyanide of potassium in 1 c.c. of water under its skin. I choose this salt because its action is exactly the same as that of free hydrocyanic acid; the potassium given in this way and in so small a quantity takes no effect whatever, as may be easily proved by a control experiment with several times as much potassium chloride. Six minutes after the cyanide of potassium has been injected, the animal's limbs are extended and paralysed, it hangs its head on one side, and tumbles over exactly as if chloral hydrate had been administered to it. But now we see something which is not caused by chlorate hydrate—twitchings of the ears and face. The respiration meanwhile is deep and regular, though reduced from 180 per minute to about 120. The heart beats regularly and strongly. I now cover the creature with a woollen cloth, so arranged, however, that we can continue to observe it. The respiration sinks gradually to 60 in the minute; the twitching already noticed resolves itself into single spasms of the whole body of short duration; but in about an hour an increase in the rate of respiration will be observable; in another hour the animal will have raised itself from its prone position, and will,

[1] See their enumeration in W. Preyers, 'Die Blausäure,' 1870, Teil ii, S. 152.

the muscles in the limbs and neck being still paralysed, remain quiet, making gradual progress towards complete recovery.

Here is another experiment, with a fatal result. 0·1 gramme of cyanide of potassium dissolved in 5 c.c. of water is injected subcutaneously in the back of a dog weighing nearly 5 kilos. Violent sickness follows in about three minutes, and the animal tumbles down unconscious. There are convulsive movements of the facial muscles and tetanic spasms of the limbs. The movements of the diaphragm meanwhile show no change either in extent or frequency, the heart beats strongly and regularly. Soon, however, the rate of respiration decreases, the pauses grow longer and longer, and the animal finally expires about eighteen minutes after the injection.

In cases of such slight or gradual poisoning we are able to analyse the process in detail: there is, first of all, narcosis of the brain, with simultaneous excitation of the motor centres of the facial muscles; then stimulation of the centres which control the extremities; exhaustion of the respiratory centre amounting at last to complete paralysis. There are no suffocative convulsions, as there is time for the hydrocyanic acid to paralyse the ganglia from which they would otherwise originate.

Very different are the symptoms when larger doses of about four times the quantity above mentioned are given. Within one or two minutes the animal becomes restless, breathes rapidly and with difficulty, drops down completely paralysed and unconscious, with violent spasms of the facial muscles, trunk, and limbs, draws a few convulsive breaths, and expires in about three minutes after the injection. The whole process takes place even more quickly and tumultuously after the inhalation of a few drops of concentrated or anhydrous hydrocyanic acid. The highly volatile acid passes at once into the pulmonary circulation, from thence in a few seconds it reaches the brain and medulla oblongata, and immediately produces the stimulating and paralysing effects above described. In human beings the process is exactly the same. It is generally asserted that the individual, after taking the poison, falls to the ground uttering

a cry as though his head was in pain. In such cases unconsciousness and general convulsions set in at once. The convulsions may be absent, as was the case in the following instance.[1] A waitress, nineteen years of age, swallowed a lump of cyanide of potassium in some coffee. She replaced the cup on its saucer, lay down near the table on which they were, covered her eyes with her left hand, and said to the servant maid who was present, "There, I have poisoned myself, and wish to die." Her breathing became audible, and in about four minutes she expired without the slightest convulsion.

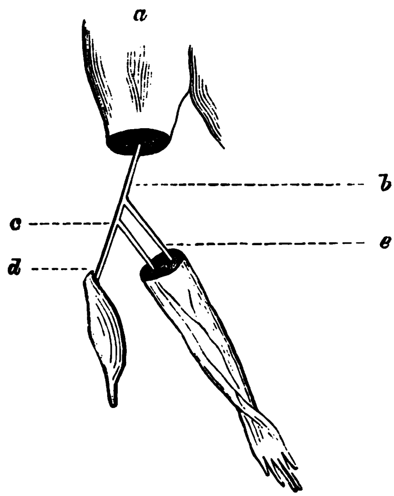
Cold-blooded animals are much less strongly affected by hydrocyanic acid and its salts. A dose of the same strength is longer in acting upon a frog than upon a warm-blooded animal. The effects produced are retarded respiration, impaired muscular movement, paralysis of the cerebrum, disappearance of reflex irritability, paralysis of the limbs, cessation of the respiration and of the heart's action; no trace of spasm or convulsion.

Of all the more important organs, the heart is the one which is least affected by hydrocyanic acid; this is the case both in warm and cold blooded animals. Its final cessation is not brought about by stimulation of the inhibitory nerves, but by paralysis of the excito-motors, for if the action of the former be eliminated by the administration of very small doses of atropine, or in the case of the frog by section of the nerves, the stoppage takes place in exactly the same manner.

What is here so very evident as regards the paralysis of the central nerve tissue is easily demonstrated with regard to the peripheral nerves. In the frog we see how, when the poison is administered internally, the paralysis of the nerve-trunks proceeds from the central parts to the periphery; if the peripheral parts are brought into direct contact with the poison they soon undergo the same change as the cerebral cortex and the motor and sensory nerves, and the muscles lose their irritability.

[1] A. Lesser, 'Atlas d. gerichtl. Medicin,' Berlin, 1883, text, S. 154; cf. also the experiments of Jörg and his colleagues in his 'Materialien,' 1825, S. 53—127.

Numerous exhaustive experiments have been made on this point.[1] The hind limb of a frog (*a*), from which the skin has been removed, can be so prepared that the thigh is



connected with the leg only by the sciatic nerve. The gastrocnemius is detached, but the afferent nerve (*c d* in the figure) is left uninjured. The muscle is then immersed in a solution of 0·7 per cent. of common salt, and the rest of the leg in a neutral solution of the same strength, to which, however, some hydrocyanic acid has been added. After a while the gastrocnemius readily responds to the stimulus of the induced current, but the vitality of the other muscles of the leg has ceased owing to their contact with the hydrocyanic acid. The stimulus of the current in the first instance sets up movements in the upper part of the body, proving that the sensory nerves of the gastrocnemius are still uninjured; when the current is applied to the leg, on the other hand, they are lacking, so that we see that the sensory nerves also have lost their irritability, and no longer respond to the stimulus. Stimulation of the sciatic nerve

[1] Kölliker, 'Arch. f. pathol. Anat.,' 1856, Bd. x, S. 272; T. E. Kiedrowski, 'De quibusdam experimentis . . . . . acidum hydrocyanicum in nervorum systema, &c.,' Doctordiss., Breslau, 1858. Under the direction of C. F. Reichert.

at *b* causes contraction of the gastrocnemius as well as reflex movements in the upper part of the body, but none in the foot; stimulation of the nerve at *e* causes no movement whatever. In short, so much of the preparation as has not been in the hydrocyanic acid remains capable of motor and sensory excitation, while that which has been steeped in it is paralysed.

The main features of the matter may be even more simply demonstrated. Here I have a frog, round both legs of which above the knee, I have tied a broad ligature, so that none of the liquid can pass into the circulation. The lower parts of the legs have been steeped for an hour in the two solutions above mentioned. I apply a powerful electric current to the toe of the "control" leg, with the result that local contractions and general indications of pain are developed. I now apply the current to the leg acted upon by hydrocyanic acid, and find it produces no effect. A little while ago I was still able to make it twitch, but by graduating the current I found, soon after the legs had been put into the solution, that a stronger current was necessary to produce contractions in the latter case than in the former.

By arranging the experiment in this simple manner, one remarkable fact was brought out very distinctly. If I now remove the ligatures and wash away the hydrocyanic acid from the leg, and then leave the animal at rest, the nervous irritability is everywhere gradually restored, just as though awakening from sleep, provided only that the amount of poison has not been too large, or the exposure of the tissue to its action has not been too prolonged.

The cessation of reflex action at an early stage is also attributed to paralysis of the sensory nerves. When it is no longer possible to excite reflex action through the periphery, it can still be done through the posterior nerve-roots of the spinal cord, and the tendency to reflex movement may still be increased by strychnine; just as stimulation of the spinal cord still produces movement, even after the frog has become motionless from general poisoning with hydrocyanic acid.[1]

[1] H. Meyer, 'Zeitschr. f. rat. Med.,' 1846, Bd. v, S. 257.

Hydrocyanic acid, even in non-poisonous doses, somewhat reduces the temperature.[1]

Hydrocyanic acid is known to produce marked effects on elementary tissues. The lowest forms of organic life, such as lymph-cells, bacteria, yeast, and hyphomycetes, are for the most part very sensitive to it. Alcoholic fermentation, for example, can easily be checked or stopped by it.[2]

Here, again, we meet with the same interesting fact that was observed in the case of the sensory nerves; the paralysis of the yeast cell appears to be no more than a sleep, unless the dose of hydrocyanic acid is too strong;[3] for, if the acid be washed out of the fermenting mixture the yeast-cells resume their activity. Butyric fermentation ceases upon the addition of 1 part in 10,000, the putrefaction of serum is prevented by 1 in 3000. Unorganised ferments, such as ptyalin and pepsin, are comparatively insensitive to hydrocyanic acid, and require larger doses to stop their action. Of course here, as in every form of decomposition or fermentation, the effect of the antizymotic is not measured solely by its quantity, but also to a great extent by the amount of the ferment, the surrounding temperature, and various other conditions under which the decomposition is effected.

The power, which has been mentioned as a property of quinine, of retarding the process of oxidation of living matter—such, for instance, as fresh protoplasm freed from its envelope—is also possessed by hydrocyanic acid. Its action in preventing the guaiacum reaction with nascent oxygen is distinctly more powerful than that of quinine.

The blood of frogs which have been poisoned with hydrocyanic acid exhibits in all parts a bright red arterial colour; this is very noticeable, on opening the chest, in the greatly distended heart, but it is even more striking in warm-

[1] Cf., among others, Hoppe-Seyler u. Salesky, the 'Med.-Chem. Untersuchungen' of the former, 1867, S. 258. In experiments on rabbits they caused a reduction of 3° C. by it. Cf. also Manasseïn, 'Rote Blutkörperchen,' 1872, S. lx.

[2] R. Fiechter, 'Der Einfluss der Blausäure auf Fermentvorgänge,' Doctordiss., Basle, 1875. Under the direction of F. Miescher.

[3] Schönbein, 'Verhandl. d. Baseler naturw. Ges.,' iii, S. 697 and 767.

blooded animals. If, after exposing a vein in the neck, and ascertaining that the blood has the usual dark colour, a strong dose of hydrocyanic acid or of potassium cyanide is given to the animal, when convulsions set in, the vein will present a bright red colour, and will be considerably dilated; and if the vein is then cut the blood will flow out in a bright red stream.[1] With the persistence of the convulsions, and the cessation of respiration, however, the blood assumes the usual dark venous colour.

By prolonged and exhaustive investigations the conditions which here come under consideration have at last been explained.[2] It has been demonstrated that, as a result of poisoning by hydrocyanic acid, the oxygen absorbed and the carbonic acid generated by the tissues are both less than the normal quantities. The reason of this is that BY THE PRESENCE OF HYDROCYANIC ACID THE TISSUES ARE DEPRIVED OF THE POWER OF ABSORBING OXYGEN. The poisoning consists in internal asphyxia of the organ in the presence of an excess of oxygen.

This furnishes a consistent explanation of the variable and often violent symptoms of poisoning with hydrocyanic acid; first there is stimulation of the nerve-centres, manifesting itself by convulsive movements, which is immediately followed by paralysis with unconsciousness and suffocative spasms, death taking place with the same rapidity as if the external supply of oxygen had suddenly been cut off, or as if very profuse hæmorrhage had occurred. Such is the course of events when comparatively large doses of the poison have been taken; after smaller doses the symptoms are the same, only differing in intensity according to the size of the dose.

Have these facts collectively or individually any practical bearing on the therapeutic use of hydrocyanic acid? I think so. Formerly this acid and its preparations were frequently administered in irritable conditions of the stomach, and particularly in cases of painful gastric ulcer; its local

[1] Cl. Bernard, 'Leçons s. l. subst. tox. et med.,' 1857, p. 195.

[2] J. Geppert, 'Ueber das Wesen der Blausäurevergiftung,' Berlin, 1889. Reprinted separately from the 15th vol. of the 'Zeitschr. f. klin. Med.' (Pharmakol. Institut of the University of Bonn).

action in paralysing the peripheral nerves indicating that it was a suitable remedy. In addition to this "sedative" action, it was said to have a "refrigerant" effect, and prussic acid was used as an antipyretic. That a slight reduction of temperature can be effected by non-poisonous doses of hydrocyanic acid is beyond question; but it has rightly been superseded by remedies and methods of a more efficacious and less dangerous character. It seems still to be occasionally used in veterinary therapeutics.[1]

Hydrocyanic acid prepared from cyanide of potassium has been systematically tested in Schrötter's clinic at Vienna, upon cases of pulmonary tuberculosis. The patients, thirty in number, had already been several weeks under treatment at the hospital, and had a high temperature and bacilli always present in the expectoration. They inhaled diluted hydrocyanic acid, in the proportion of 2·5 cg. to 1 cubic metre of air (about $\frac{1}{3}$ of a drop to a cubic yard of air). These experiments showed that the patients became tolerant of the remedy, so that the quantity could be gradually increased. After using the inhalation for one or two days the fever disappeared, and in about ten days the night sweats ceased; the pulse went down from 100 or 120 to 60 or 80, the cough became less violent, and twenty of the patients gained in weight. There was no change in the lung itself, it was only the symptoms which were modified.[2]

The only preparation containing hydrocyanic acid now officinal in Germany is the AQUA AMYGDALARUM AMARARUM. It is a transparent or nearly transparent liquid, with a strong odour of hydrocyanic acid and oil of bitter almonds. This odour should persist even when the hydrocyanic acid has been precipitated by nitrate of silver. Water of bitter almonds should contain $\frac{1}{10}$ per cent. of prussic acid. It is prepared from bitter almonds; they are first pounded as finely as possible, the fatty oil is then separated by strong pressure, the almond cake is then heated in a steam bath and distilled with water and a small amount of alcohol. On heating the almonds the albuminoid substance, emulsin,

[1] Fröhner, ref. 'Cbl. f. d. med. Wiss.,' 1887, S. 640; also 'Lehrbuch der Arzneimittellehre,' by the same author, 1890, S. 108.

[2] Koritschoner, ref. 'Cbl. f. klin. Med.,' 1891, S. 295.

contained in them acts as a ferment on the crystallisable acid amygdalin, decomposing it, and, with the addition of water, forming oil of bitter almonds and hydrocyanic acid:

$$\underset{\text{Amygdalin.}}{C_{20}H_{27}NO_{11}} + \underset{\text{Water.}}{2H_2O} = \underset{\text{Glucose.}}{2C_6H_{12}O_6} + \underset{\text{Oil of bitter almonds.}}{C_7H_6O} + \underset{\text{Hydrocyanic acid.}}{HCN.}$$

By this process the glucose and oil of bitter almonds are separated from the hydrocyanic acid, though a small quantity of the oil passes over in the distillate. This does not, however, interfere with the action of the bitter almond water; if anything, it rather promotes it. The oil, chemically, is benzoic aldehyde, $C_6H_5.COH$, the aldehyde of benzoic acid, $C_6H_5.COOH$, and was formerly officinal. As commonly sold it usually contains some hydrocyanic acid, which can be separated from it by agitation with chalk and ferrous chloride. When freed from the acid it is not more poisonous than most other ethereal oils. It can also be prepared artificially from benzol.

The kernels of cherries, plums, peaches, apples, and other fruits contain amygdalin and emulsin, and consequently hydrocyanic acid and benzoic aldehyde are formed, when the kernels are pounded down and mixed with lukewarm water.

The officinal water of bitter almonds contains a small quantity of alcohol, which is purposely added in order to preserve it from decomposition. Aqueous solutions of hydrocyanic acid and its salts quickly turn brown, and are then found to contain, together with unknown bodies, some ammonium formate resulting from the following decomposition: $HCN + 2H_2O = NH_4.CHO_2$. The addition of a little mineral acid checks this decomposition. It is owing to this instability of hydrocyanic acid that the Pharmacopœia directs that it should not be exposed to the light.

The maximum single dose of bitter almond water is 2 grammes (30 minims), which corresponds to 0·002 gramme ($\frac{1}{38}$ of a drop) of anhydrous hydrocyanic acid. The presence of hydrocyanic acid in this preparation can be easily demonstrated. I add a very small quantity of solution of potash, whereby the acid is converted into potassium cyanide; next, a little ferrous sulphate, converting the potassium cyanide

into potassium ferrocyanide (the yellow ferrocyanide); and then a little ferric chloride, thereby forming ferric ferrocyanide (Prussian blue), which is immediately precipitated upon the addition of a free acid (hydrochloric). The free acid also dissolves the precipitate formed by the alkali from the ferrous and ferric salts, the Prussian blue alone remaining undissolved. The following formulæ represent the above changes:

(i) $HCy + KHO = H_2O + KCy$;

(ii) $6KCy + FeSO_4 = K_2SO_4 + K_4FeCy_6$;

(iii) $3K_4FeCy_6 + 2Fe_2Cl_6 = 12KCl + Fe_7Cy_{18}$;

the last consisting of $3FeCy_2$ and $2Fe_2Cy_6$.

The medicinal use of bitter almonds was known to the ancients, for Dioscorides[1] recommends them as an external application for putrefying sores, and as an internal remedy to alleviate pain, to increase the flow of urine, to promote sleep, and for many other purposes. He says that they were also used to kill foxes, being mixed with other kinds of bait which the animals eat.

If Aqua Lauro-cerasi, cherry-laurel water, is prescribed by the physician, the chemist generally supplies bitter almond water. The cherry-laurel water, made from the leaves of *Prunus lauro-cerasus*, was also formerly officinal. These leaves contain amorphous amygdalin, and have been recognised as poisonous since 1728, when some females in Dublin took them, medicinally, in too large doses, with fatal results.[2] Several experiments were consequently made soon after on dogs. The animals died with all the symptoms of poisoning from prussic acid.

Cases of poisoning with this acid are not infrequent, as cyanide of potassium is almost indispensable in various arts, such as electro-plating and photography, and is therefore easily obtained. We sometimes hear of prussic acid and potassium cyanide being used in chemical laboratories for suicidal purposes. The poisonous effects of bitter almonds, cherry-laurel leaves, and the kernels of some of our native fruits have rarely to be considered, as, owing to the taste,

[1] 'Materia medica,' lib. i, cap. 176.

[2] T. Madden, "On the Poisonous Quality of Laurel Water," 'Philosoph. Trans.,' London, 1734, vol. vi, part 2, pp. 365—378.

they are not often accidentally swallowed. One case, however, occurred in which a woman with suicidal intention ate nearly 72 grammes (nearly 2½ ounces) of bitter almonds. In ten minutes she dropped down unconscious, and in an hour and a half expired. The reporter[1] estimates that the 72 grammes probably would contain about 2·88 grammes of amygdalin, and that from this upwards of 0·19 gramme (2·9 grains) of anhydrous hydrocyanic acid could be obtained, which is very much more than enough to cause death.

When vegetable substances are swallowed which contain amygdalin, the decomposing ferment being always present as well, hydrocyanic acid is very quickly developed in the stomach. But after swallowing amygdalin alone, poisonous effects are developed much more slowly, for the stomach does not always contain the necessary ferment, and decomposition of the amygdalin does not then occur until it is acted on by the pancreatic juice.

In most cases of hydrocyanic acid poisoning the physician arrives too late, owing to its rapid and violent action. But it sometimes happens that the amount taken is too small to kill, or that the presence of a large quantity of food in the stomach weakens its action. The poisonous effects are then modified, and there is consequently a possibility, by proper treatment, of saving life. We must endeavour at once to prevent what constitutes the chief danger, and that is the tendency to paralysis of the respiratory organs. All the means which I have already described must here be employed, and especially the warm bath at 38° C. (100·4° F.) in conjunction with douches of ice-cold water at intervals. In cases apparently hopeless, when the respiration has even fallen to 2 in the minute, recovery may still take place under this treatment.[2]

Very remarkable is the statement made by one familiar with the business,[3] that electro-platers, who use large quantities of potassium cyanide in their work, and consequently always have a strong odour of hydrocyanic acid about them,

[1] Maschka, 'Wien. med. Wochenschr.,' 1869, S. 838.

[2] Mueller-Warneck, 'Berl. klin. Wochenschr.,' 1878, No. 5; Quintin, ibid., 1885, No. 8.

[3] R. Reuter, ref. 'Wiener med. Wochenschr.,' 1890, S. 1247.

suffer no inconvenience from it, but, on the contrary, are exceptionally healthy. In another report, however, a different opinion is expressed.[1]

In poisoning with cyanide of potassium, taken by the mouth, its caustic action should be noted. This is due to the prussic acid being a very weak acid, and not neutralising the potash, which consequently retains its caustic properties; and also to the excess of caustic potash or of potassium carbonate, which the commercial potassium cyanide generally contains. Moist cyanide of potassium smells of hydrocyanic acid, the latter being continuously displaced and liberated by the carbonic acid in the atmosphere.

The changes which hydrocyanic acid or potassium cyanide undergo in the body, have not as yet been determined. It has been maintained that they undergo no change, since large quantities have repeatedly been recovered from the body after death. It is, moreover, experimentally demonstrable that,[2] without undergoing any change themselves, they are able, by decomposing water into H and OH, to induce other chemical changes, which consist in the simultaneous oxidation and reduction of organic molecules. The bodies of persons poisoned by hydrocyanic acid often have the characteristic odour of the acid.

I will here observe, by the way, that cyanogen gas $(CN)_2$ is less poisonous than hydrocyanic acid. Of the latter, 0·004 gramme subcutaneously injected is certain to kill a cat, but 0·02 gramme of cyanogen is required to produce the same result. The action of cyanogen is less violent and more gradual, and there are apparently no convulsions arising from direct irritation of the brain; the cause of death is paralysis of the respiratory organs supervening upon dyspnœa.[3]

Potassium ferrocyanide, yellow ferrocyanide of potash,

[1] A. Martin, "Ein Fall von chronischem Siechtum, hervorgerufen durch Einatmung von Blausäure," reprinted separately from Friedreich's 'Blätter f. gerichtl. Med. und San. Polizei,' 39th annual series, 1888.

[2] O. Wallach, 'Berichte der deutschen chem. Ges.,' 1877, Bd. x, S. 2120.

[3] B. Bunge, 'Arch. f. exper. Pathol. u. Pharmak.,' 1880, Bd. xii, S. 41.

K_4FeCy_6, formerly officinal, was held to be non-poisonous, and to have simply a cathartic action, like Glauber's salts. This may be the case under ordinary circumstances, for, though when it is heated with dilute acids, hydrocyanic acid is liberated, the gastric acid is not sufficient to effect this. On the other hand, hydrocyanic acid has been liberated from it by the action of nitro-hydrochloric acid[1] and of tartaric acid.[2] The latter occurred in the case of an individual who committed suicide by swallowing a solution of potassium ferrocyanide and directly afterwards one of tartaric acid, and died "immediately after, with symptoms of poisoning from concentrated hydrocyanic acid." It seems possible to me that a similar result might be brought about by casually taking a larger quantity than usual of the other acids either in our food or drink; and therefore I cannot concur in the statement made in handbooks that the action of ferrocyanide of potash does not differ from that of Glauber's salts. There is, moreover, another reason why the action should differ; the commercial yellow potassium ferrocyanide, owing to the way in which it is manufactured, is invariably adulterated with potassium cyanide.

[1] Volz, 'Vierteljahrschr. f. gerichtl. Med.,' 1877, Bd. xxvii, S. 57.

[2] F. L. Sonnenschein, 'Handbuch d. gerichtl. Chemie,' 1881, S. 162.

XXVI.

The free acids—Their action upon the pulse, the temperature, and upon the bodily fluids—Their various organic and inorganic preparations, contained in the Pharmacopœia—The nitrates of potash and soda.

EXPERIENCE has long since taught us that persons in a febrile condition crave for acid drinks and fruits, and have a repugnance to alkaline solutions, the taste of the latter being even more disagreeable to them than to persons in health. Consequently, down to the present time, mineral and vegetable acids have been established remedies in fever, and are classed among the refrigerants.

This view is supported by physiological facts. The blood and lymph have an alkaline reaction; the various forms of disintegration and oxidation take place mainly in tissues through which an alkaline carbonate continuously flows; investigations with regard to the metabolism of the tissues show that it is increased under the action of an increased amount of alkali; and all these facts seem to justify the conclusion that if the alkalescence of the bodily fluids be lessened, the processes of disintegration and oxidation are thereby retarded.

Numerous investigations have been made with regard to the action of free acids on warm-blooded animals. I leave out of consideration all those in which large and caustic doses have been introduced into the stomach, as well as those in which smaller amounts have been injected into the blood. Observations made in such a fashion are solely of toxicological interest, and furnish no results with which we need concern ourselves. Kobert took 10 grammes (2½ drachms) of anhydrous phosphoric acid within sixteen

minutes, with 90 grammes of syrup and 200 grammes of water. This was followed by a slight decline in the frequency of the pulse and of the temperature, the latter sinking 0·9° C. (1·6° F.) between 4 and 10 p.m., which exceeds by 0·5° C. (0·9° F.) the usual fall in human beings. The most important point seems to be, that no other alteration in the general state of health was noticed after taking these 10 grammes of anhydrous phosphoric acid. The acidity of the urine was increased. Similar results were obtained from experiments on two other persons.[1] From a subsequent series of experiments,[2] made by giving smaller doses of phosphoric acid for a considerable period, the opposite result as regards the pulse, was obtained; the frequency was increased, or at first it was diminished and then increased so long as the acid was taken, and the increase continued for some time after the acid had been discontinued.

Investigations as to the action of free carbonic acid[3] were made at an earlier date. Effervescing powder[4] was taken in water. The maximum reduction of the pulse was sixteen beats in the minute; the duration of this slow rate averaged 20 minutes; the temperature fell 0·1° to 0·3° C. (0·18° to 0·5° F.), and remained so for nearly thirty minutes. The same effect was observed[5] after the administration of 2·64 grammes of carbonic acid in 630 c.c. of water; the pulse fell from 80 to 72, the temperature from 36·9° to 36·5° C. (98·4° to 97·7° F.) in twenty minutes; and similar results were obtained in two other experiments. Drinking the same quantity of ordinary water, under the same conditions, did not produce these changes. The writer also adds his opinion, that the depressing effect upon the pulse lasts at least as long as the urine (which he drew off from time to time by the catheter) contains more than the normal amount of this gas; and accordingly the depression becomes most

[1] Kobert, 'Jahrbücher d. ges. Med.,' 1878, Bd. clxxix, S. 225.

[2] Hugo Schulz, 'Therapeut. Monatshefte,' 1891, S. 126.

[3] Lichtenfels und Fröhlich, "Beobachtung über Puls und Korperwärme in den normalen Zuständen sowie unter dem Einflusse bestimmter Ursachen," 'Denkschr. d. k. k. Akad. d. Wiss.,' Wien, 1852, Bd. iii, S. 113.

[4] Bicarbonate of soda, 10 parts; tartaric acid, 9 parts; sugar, 19 parts.

[5] G. Kerner, 'Arch. f. d. ges. Physiol.,' 1870, Bd. iii, S. 151.

marked half an hour or an hour after taking tolerably strong doses.

So much with regard to the action of free acids upon the pulse and temperature. The effect of non-poisonous doses of sulphuric acid, in reducing the alkalinity of the blood,[1] have also been tested. Before and after the introduction of the acid, blood was taken from a vein, and the serum tested by Zuntz's method. The experiments proved beyond doubt that the alkalinity of the blood, in various animal species, is diminished by the introduction of dilute sulphuric acid into the stomach, and, consequently, that the organism furnishes bases for its neutralisation. For instance, the alkalinity of the blood was reduced in one case 35, and in the other 38 per cent. in the course of two days. Other experiments,[2] moreover, demonstrated that the amount of carbonic acid in the blood of such animals is reduced considerably; that it is impossible to neutralise all the alkali in the blood of mammals during life; that a very great reduction of alkalinity paralyses the respiratory centre; that in poisoning with acids, when carefully managed, the introduction of soda will bring about the complete recovery of the moribund animal; and that in dogs and human beings the organism, by furnishing a considerable increase of ammonia, which passes off in the urine, neutralises about three fourths of the acid administered. This neutralisation did not take place in herbivora (rabbits), and the diminished alkalinity was consequently much more marked in their case. It is assumed that this ammonia is what would otherwise be used for the synthetic formation of urea in the body.

As far as I am aware, no exact observations have been made on the action of acids upon febrile patients. We will now consider the various PREPARATIONS, and in so doing we shall have occasion to discuss some points which are unconnected with the treatment of the febrile condition, but which are of interest therapeutically.

ACIDUM SULPHURICUM, sulphuric acid, H_2SO_4. A colourless and odourless liquid, of oily consistence, volatilising when

[1] O. Lassar, 'Arch. f. d. ges. Physiol.,' 1874, Bd. ix, S. 44.

[2] F. Walter, 'Arch. f. exper. Pathol. u. Pharmak.,' 1877, Bd. vii, S. 148.

heated, having a specific gravity of from 1·836 to 1·840, and containing from 94 to 97 per cent. of real sulphuric acid. The remainder is water.

Acidum Sulphuricum Dilutum, dilute sulphuric acid. Specific gravity from 1·110 to 1·114. It consists of one part of rectified acid mixed with five of water.[1] From one to three drops may be taken in water, mixed with some palatable syrup, or one part of the dilute acid may be mixed with 100 parts of water and 20 parts of raspberry syrup, of which a tablespoonful may be taken every two or three three hours. For delicate stomachs, mucilage of some sort may be substituted for the syrup.

Mixtura Sulphurica Acida, Haller's acid. This consists of three parts of rectified spirit and one of strong sulphuric acid. It is a clear colourless liquid, the specific gravity of which is from 0·993 to 0·997. This compound is still held in high repute in many quarters, probably owing to the great name it bears.[2] It contains ethyl-sulphuric or sulphovinic acid, $C_2H_5.HSO_4$, concerning the special action of which we have at present no information. The remedy is given in somewhat smaller doses than the Acidum Sulphuricum Dilutum, and in the same manner.

There is a special point with regard to the pharmacotherapeutics of sulphuric acid, which, if neglected, may under some circumstances be prejudicial to the patient. Its presence in small quantities favours the development of mould (hyphomycetes) in medicinal solutions. I myself have called attention to this fact, and have proved it experimentally.[3] I have also seen patients who were being treated with the vitiated medicines, especially when the latter were expensive, the "sediment" or "mucus" being regarded as of no importance.

Put 150 c.c. of ordinary distilled water into each of two glass-stoppered bottles, which have been previously well washed out with water, also distilled. To the water in one

[1] This is more than twice the strength of the Acidum Sulphuricum Dilutum P.B., the sp. gr. of which is 1·094.—Transl.

[2] A. v. Haller, 1708–77, Professor at Göttingen and Berne.

[3] C. Binz, 'Arch. f. pathol. Anat.,' 1869, Bd. xlvi, S. 78; also, by the same author, "Ueber Pilze in arzneilichen Flussigkeiten," 'Wiener med. Presse,' 1880, S. 866 und 898.

bottle, add one drop of concentrated sulphuric acid. Let both vessels be closed hermetically and put into a room at a temperature of about 20° C (68° F.), and leave them undisturbed for about two months. If the bottles are then slightly rotated, no change will be observable in the pure water; whilst at the bottom of that to which the sulphuric acid was added small flakes will be seen which, upon microscopical examination, prove to be fungoid mycelia.

How is it that sulphuric acid promotes the development of fungi? I think the answer is this: fungoid formations, like all living organic cells, consist of albumen, and albumen invariably contains sulphur. Fungoid germs exist everywhere in the unfiltered air and unboiled water, in the neighbourhood of human dwellings. They find the elementary constituents of albumen in the dead particles of dust in the air. They attack with avidity any sulphur compound, as is proved by their rank development in the presence of sulphuric acid and some organic substances. Hyphomycetes are powerful reducing agents. They abstract the oxygen and sulphur from sulphuric acid, and live upon both. The intermediate development of sulphuretted hydrogen in mineral waters containing sulphates, when put into dirty bottles, is a well-known occurrence; it is developed by these processes.

From these facts it is obvious what effect sulphur may have on any preparations and compounds which, in the process of manufacture, happened to be contaminated by the presence of sulphates. The former professor of botany at Bonn, v. Hanstein, once handed me a solution, made according to a prescription, of 6 parts of potassium bromide in 150 parts of water, remarking at the time that it could not be pure, as a thick layer of *Protococcus vulgaris* had very quickly been developed at the bottom of the bottle; he further wished to know whether it was safe to get any more potassium bromide from the same quarter. I at once suspected that the drug was contaminated with sulphuric acid, and this on investigation proved to be the case. I then made a strong solution of potassium bromide, which I obtained in fine large cubic crystals from another local chemist, and tested it with barium chloride. Barium

sulphate was immediately precipitated.[1] The presence of sulphuric acid is explained by the fact that it is one of the substances employed in the manufacture of the various preparations.

Medicinal solutions used as lotions for the eyes may, if mouldy, do harm rather than good.[2] They should therefore, after being prepared, be sterilised by boiling.

ACIDUM PHOSPHORICUM, phosphoric acid, H_3PO_4. The officinal preparation is a clear colourless and odourless liquid, consisting of 25 per cent. of the pure acid, and 75 per cent. of water. Both in taste and in its local and general effects it is milder than the other mineral acids. It does not coagulate albumen. The dose and method of administration are the same as in the case of Acidum Sulphuricum Dilutum.

ACIDUM HYDROCHLORICUM, Acidum Muriaticum, hydrochloric or muriatic acid, HCl. This is a clear, colourless liquid, volatilising when heated, and containing 25 per cent. (32 per cent.—Ph. B.) of the pure acid in water.

Hydrochloric acid, being one of the factors in gastric digestion, is specially useful in that form of dyspepsia which is accompanied with heartburn, sour eructations, flatulence, &c., and arises from a deficiency in the amount of gastric juice, or from the presence of some abnormal product of decomposition. This acid also relieves the dyspepsia which accompanies febrile conditions, when, according to Manasseïn, there is a deficiency in the amount, not of pepsin, but of free acid.[3] Pepsin is only efficacious in an acid solution; the acid is taken up by the peptones, and must be artificially supplied if the stomach does not secrete it in sufficient quantity. At a temperature of 40° C. (104° F.) hydrochloric acid is itself capable of dissolving—though slowly—fibrin which has been cooked, and converting it into

[1] For further information on the subject of the development of fungi in medicinal fluids see vol. i, p. 266, as well as M. Rosenthal, 'Ber. d. Gesellsch. d. Aerzte zu Wien,' 5 März, 1880; A. Hiller, 'Zeitschr. f. klin. Med.,' 1881, Bd. iii, S. 221.

[2] J. Hirschberg, 'Berl. klin. Wochenschr.,' 1885, S. 668; G. Abbot, 'Lancet,' 1885, i, p. 315.

[3] Manasseïn, 'Centralbl. f. d. med. Wissensch.,' 1871, S. 852; 'Arch. f. pathol. Anat.,' 1872, Bd. lv, S. 451.

peptone.[1] It is sometimes effectual, when administered for a considerable period, in curing chlorosis.[2]

The dose of hydrochloric acid is about 3 drops diluted with water, two or three times a day; for continuous use 1 part may be mixed with 150 parts of syrup, to which, with advantage, some simple bitter may be added; or 2 to 4 parts of the acid may be mixed with 200 parts of water, a tablespoonful being taken a quarter of an hour after each meal. Of ACIDUM HYDROCHLORICUM DILUTUM double the dose should be taken, as it is merely a mixture of equal parts of muriatic acid and water.

The following preparation is often administered in conjunction with hydrochloric acid:

PEPSINUM, pepsin, a fine whitish powder which is slightly hygroscopic, and has a peculiar odour and slightly saline taste. When 1 part is mixed with 100 parts of water it forms a somewhat cloudy solution, which has a scarcely perceptible acid reaction. If 10 grammes (150 grains) of hard-boiled white of egg, coarsely minced, be mixed with 100 c.c. (3½ ounces) of water at 50° C. (122° F.), 10 drops of hydrochloric acid, and 0·1 gramme (1½ grains) of pepsin, then repeatedly agitated and allowed to stand in a temperature of 45° C. (113° F.), at the end of an hour all but a few shreds should be dissolved.

Pepsin is used chiefly in cases of chronic gastric catarrh, in doses of 0·1 to 0·5 gramme (1½ to 7½ grains) in powder or solution, with or without hydrochloric acid. Owing to its power of dissolving albumen, it is also utilised, either as a local application or injected into the tissues, for the purpose of destroying membranes, tumours, or ulcerated surfaces. In these cases, however, the results are less encouraging than those following its use in derangements of the digestive function.

VINUM PEPSINI, pepsin wine, is a mixture of 24 parts of pepsin, 20 of glycerine, 3 of hydrochloric acid, and 20 of water, which is allowed to stand with occasional agitation for eight days, after which 92 parts of treacle, 2 of tincture of orange, and 839 of sherry wine are added, making alto-

[1] Wolffhügel, 'Arch. f. d. ges. Physiol.,' 1873, Bd. vii, S. 188.
[2] Zander, 'Arch. f. pathol. Anat.,' 1881, Bd. lxxxiv, S. 177.

gether 1000 parts. It acts, as its composition indicates, as a stimulant on the stomach. The dose is from a teaspoonful to a tablespoonful.

Aqua Chlorata, Liquor Chlori, chlorine water, is a clear yellowish-green liquid of suffocating odour, dissipated by heat, and immediately discharging the colour of blue litmus paper. It should contain not less than 4 per cent. of chlorine. When given in very small doses (2 to 10 drops in water) it is supposed, on reaching the stomach and coming in contact with tissues which contain hydrogen, to be converted into hydrochloric acid. It was formerly largely used internally, as an antiseptic remedy, in infectious fevers, —such, for instance, as enteric fever; but we can hardly suppose that the slightest trace of it penetrates to the lower part of the small intestine, where the typhoid poison is chiefly generated. Its use, consequently, in these disorders has, to a large extent, been abandoned. The chlorine in Aqua Chlorata is gradually dissipated under the action of light and air, the solution should therefore be freshly prepared.

Acidum Nitricum, nitric acid, HNO_3. A clear colourless liquid, volatising with heat, containing 25 per cent.[1] of real nitric acid mixed with water. Nitric acid coagulates albumen more quickly than any other acid, and is intensely corrosive. On this account the use of it has been almost discontinued in Germany, but not in England. I will therefore quote to you the statements of an English authority[2] with regard to its therapeutic properties. "Internally the dilute acid is used to quench thirst in febrile conditions, like other dilute acids, and it is useful in cases of dyspepsia. It is supposed to have an action upon the liver, and certainly appears to be of use in cases of so-called biliousness. When absorbed it has an astringent action, and is exceedingly serviceable in diminishing the secretion from the lungs in bronchitis, and in the subacute exacerbations of phthisis. It is also employed in cases of syphilis occurring in debilitated subjects,

[1] The Acidum Nitricum, Ph. B., contains 70 per cent. of real nitric acid. The Acidum Nitricum Dilutum, Ph.B., 17·44 per cent.—Transl.

[2] T. Lauder Brunton, 'Text-book of Pharmacology, Therapeutics, and Materia Medica,' 1887, pp. 575 and 576.

where mercurials are not well borne. It diminishes phosphatic deposits in the urine, and, in a dilute condition, has been injected into the bladder in order to dissolve calculi already formed."

In the same work (p. 403) the combination of nitric acid with hydrochloric acid (nitro-hydrochloric acid[1]) is said to have a special action on the liver, and to promote the secretion of bile.

In prescribing nitric acid the dose at first should be two drops in half a wine-glassful of water, and may afterwards be cautiously increased.

Two nitrates may be discussed here, Kalium Nitricum and Natrium Nitricum. Both were formerly much prescribed as antifebrile remedies, but this is no longer the case; one of them is still occasionally used as a poison, and both present some points of scientific interest.

Potassium nitrate, or saltpetre, KNO_3, consists of colourless, transparent, prismatic crystals, or of a crystalline powder. It is soluble in four parts of cold water, and in less than half its own weight of boiling water, but is almost insoluble in alcohol.

For a long period it had the reputation of being a cooling medicine. "Refrigerat," writes Haller,[2] "et sanguinem tenuem et fluidum reddit, alvum laxat, ulcera cacoethica curat." It was supposed to liquefy the fibrin of inflammatory exudations in acute inflammation of the lungs and similar maladies, to free the blood from any excess of fibrin which would tend to produce inflammation, and to diminish excessive action of the heart in acute fevers,—for this excessive action was held to be the cause, not the result, of increased combustion in the organism.

Careful investigation has not confirmed these views, and nitrate of potash is now little employed as a remedy. In one preparation only is it still used. This is the officinal Charta Nitrata, nitre-paper, made by soaking blotting-paper in a solution of 1 part of nitrate of potash to 5 of water, and then drying it. When ignited it smoulders,

[1] This acid contains free chlorine, hydrochloric, nitric, and nitrous acids.

[2] A. v. Haller, 'Bibl. medica pract.,' 1794, Bd. iii, S. 550.

giving off fumes which, inhaled, often afford the most decided relief to asthmatic patients. It is impossible to tell beforehand what forms of asthma it will suit; on many it has not the slightest effect. Neither do we know in what way the soothing effect is produced. In the fumes have been found[1] ammonium carbonate, upon which its strong alkaline reaction depends, together with empyreumatic and aromatic substances, one of which smelt of oil of bitter almonds, and another when oxidised smelt strongly of cumarin. Cyanogen compounds and potassium nitrite, which were formerly supposed to be present, could not be detected.

We will now further discuss the action of saltpetre. Jörg experimented on himself and his pupils with it, and the only "definite" effects that he found it to possess were as follows: it increased the secretion of urine—even when no larger quantity of water than usual was taken—it set up inflammation throughout the whole of the intestine, and it induced eczematous eruptions. In one instance 7·2 grammes (110 grains) were taken when the stomach was almost empty, whereupon the above symptoms showed themselves and lasted for three days.[2]

Larger doses not infrequently produce fatal results. Falck collected the reports of twenty cases, in nine of which death occurred.[3] In eight of them saltpetre was taken by mistake for Glauber's or Epsom salts, in one for common salt, in two cases the accidental poisoning was due to other mistakes; in one an enema contained an overdose of nitre, and in the remainder the dose prescribed had been too large. The immediate cause of death was probably gastro-enteritis, which Buchheim considers is due to diffusion.[4] If a concentrated solution of saltpetre, which is the most rapidly diffusible of all the officinal potassium or sodium salts, comes in contact with a vascular animal membrane, the arterial pressure in the capillaries will be overpowered by the force of the diffusion stream passing inwards. The blood-serum being then replaced by a smaller quantity

[1] W. Kochs, 'Centralbl. f. klin. Med.,' 1886, S. 689.
[2] Jörg, loc. cit., S. 28—52.
[3] Falck, 'Lehrbuch d. prakt. Toxikologie,' 1880, S. 115.
[4] Buchheim, 'Arch. f. exper. Path. u. Pharmakol.,' 1875, Bd. iii, S. 252.

of the saline solution, the blood-corpuscles in the capillaries will accumulate to such an extent that some of them will be forced through the capillary walls, and so hæmorrhagic erosions will be produced. These effects can, of course, be prevented or lessened by distending the stomach with liquid, or by largely diluting the solution of nitre.

Paralysis of the central organs from large doses of potassium nitrate may depend, in the first place, upon violent reflex irritation starting from the viscera, which, especially if inflammation[1] exists, reacts strongly upon the heart; or it may be due to the abnormal amount of potassium which finds an entrance into the circulation through the relaxed vessels; and finally, we must not overlook the possibility of the reduction of the nitrate, even if only to a small extent, into the poisonous nitrite. The subject, as yet, has not been thoroughly investigated.

SODIUM NITRATE, cubic nitre, or Chili saltpetre, $NaNO_3$, consists of colourless, transparent, rhomboidal crystals, which are deliquescent, but are stable in dry air, and have a bitter saline cooling taste; they are soluble in 1·2 parts of water, and in 50 of rectified spirit. Sodium nitrate is called Chili saltpetre because it is found in large beds on the borders of Chili and Peru. It is also called cubic nitre, the blunt rhombohedra belonging to the hexagonal system having been mistaken for cubes.

Sodium nitrate was for a long time used medicinally in the place of potassium nitrate. A tablespoonful of a solution containing 15 parts of this salt in 200 parts of water, taken every two hours, was until about twenty years ago the ordinary prescription of many physicians for the treatment of inflammation, or for the prevention of traumatic fever. Its use for these purposes was based on the same assumptions as in the case of potassium nitrate, over which it possessed the advantage of not being POISONOUS.

Experiments on healthy subjects with sodium nitrate were undertaken about 1847 by Löffler,[2] of Berlin. After the

[1] J. Tarchanoff, 'Gaz. méd. de Paris,' 1875, S. 180.

[2] Löffler, 'Jahrb. der gesammten Medicin,' 1848, Bd. lx, S. 18; Rademacher, 'Grundzüge der Erfahrungsheillehre,' 1848, 3 Ausg., Bd. ii, S. 16—204.

administration of somewhat less than 90 grammes (about 3 ounces) in eight days, the subjective condition was only slightly, if at all, affected, but marked symptoms showed themselves if the drug was continued for a longer time. The most noticeable of these were general lassitude and constant inclination to sleep, which however was not refreshing, and did not relieve the feeling of fatigue; a diminution in the frequency and strength of the pulse; and an increased flow of urine. Another series of experiments [1] corroborated these results in all their essential details.

The question as to the action of the drug in increasing the secretion of urine has also been discussed in a subsequent work.[2] If, in consequence of disturbances of the circulation caused by large doses of chloral hydrate, the secretion from the kidneys ceased, it could again be restored by sodium nitrate. The urine, which was then secreted in "considerable quantities," was generally of a red colour, owing to the hæmoglobin dissolved in it. This increased secretion is due solely to the action of the salt upon the tissue of the kidneys, a point I shall again refer to in discussing the action of diuretic remedies.

Sodium nitrate, if injected into the vessels of a muscle during its contraction, is converted into sodium nitrite, $NaNO_2$.[3]

I was led to make some experiments with reference to sodium nitrate, in consequence of being asked how it is that this salt, which when used medicinally rarely gives rise to any poisonous symptoms, should produce acute symptoms of poisoning in many animals simultaneously, from being accidentally swallowed instead of ordinary salt (sodium chloride) on pastures where it is used as manure.

Instances of this kind are not uncommon. The researches of one of my pupils[4] led to the following results.

[1] Schirks, Doctordiss., Greifswald, 1856, according to Schuchardts, 'Arzneimittellehre,' 1858, S. 374.

[2] P. Grützner, 'Arch. f. d. ges. Physiol.,' 1875, Bd. xi, S. 370.

[3] Gscheidlen, 'Arch. f. d. ges. Physiol.,' 1874, Bd. viii, S. 506. Cf. also Schönbein, 'Journ. f. prakt. Chem.,' 1861, Bd. lxxxiv, S. 193; 'Zeitschr. f. Biologie,' 1867, Bd. iii, S. 337.

[4] A. Barth, 'Toxikologische Untersuchungen über den Chilisalpeter,' Doctordiss., Bonn, 1879.

Pure sodium nitrate is always reduced, at least partially, to the poisonous nitrite, when such things as oats, endive, or raw potatoes are rubbed up with it in water, and then digested at blood-heat for a few hours. The same thing happens if mixed with blood outside the body, methæmoglobin being formed at the same time. A similar reduction also of the nitrate generally takes place if 1 c.c. of a 10 per cent. solution is injected into an intestinal loop tied at both ends, and then replaced in the abdomen for about an hour. The intestinal mucous membrane becomes thereby ecchymosed and swollen. This effect may also be produced in animals which have swallowed the nitrate, and the nitrite can then be detected in the fresh urine. This reduction is probably due to the presence of putrefactive ferments in the intestine. When the nitrate is absorbed in the upper part of the alimentary canal, and so does not come in contact with these ferments, it passes unchanged through the system, and without giving rise to any poisonous symptoms.

CARBONIC ACID is in an intermediate position between the inorganic and the organic acids. We are here only concerned with its effects, when taken in various mineral waters, obtained either from natural sources or artificially prepared. These have largely superseded the solutions, or waters, of former times, though the following are still officinal in Germany. POTIO RIVERI, River's drink, a recently prepared solution of 4 parts of citric acid in 190 of water, to which 9 parts of carbonate of soda are then added; and the two effervescent powders—(1) the ordinary PULVIS AËROPHORUS, consisting of 10 parts of sodium bicarbonate, 9 of tartaric acid, and 19 of sugar; and (2) PULVIS AËROPHORUS ANGLICUS, in which 2 grammes (30 grains) of sodium bicarbonate and 1·5 grammes (22½ grains) of tartaric acid are dispensed in packets of different coloured papers, each powder to be

separately dissolved in eau sucré, the two solutions then mixed and drunk while effervescing. The latter form is the best; the first-named powder is deliquescent, and the carbonic acid is consequently dissipated.

Beverages which contain carbonic acid are diuretic,—that is to say, the secretion of urine is subsequently larger than after taking the same quantity of plain water. This results from the more rapid absorption by the intestines of the aërated beverage.[1] It is possible that the more rapid intestinal absorption may itself result from the hyperæmia of the mucous membrane induced by contact with the carbonic acid. This hyperæmic condition of the mucous membrane, induced by the carbonic acid, can readily be observed on examining the gums and mouth, and was very manifest in the gastric mucous membrane of a dog with a fistula, and was all the more striking in this case because, the dog having been bled, the gastric mucous membrane was previously paler than usual.

Introduced into the stomach of human beings, either as gas or in solution in water, carbonic acid increases the secretion of hydrochloric acid and pepsin.[2] The respiratory movements become deeper and slower under the reflex stimulation of beverages containing this gas.

Of the organic acids belonging to this class the following are officinal.

ACIDUM ACETICUM, acetic acid, $C_2H_4O_2$, or $CH_3.COOH$. This is a clear, colourless, volatile liquid, having a pungent acetous odour and strong acid taste. It mixes in all proportions with water, alcohol, and ether, and crystallises when cooled; it boils at 117° C. (242·6° F.); its specific gravity is 1·064, and it contains 96 per cent. of real acid. When diluted so as to contain only 30 per cent. of real acid it is the ACIDUM ACETICUM DILUTUM of the German Pharmacopœia; diluted so as to contain only 6 per cent. of real acid it corresponds with the officinal ACETUM, vinegar, though vinegar, as a matter of fact, is generally manufactured by a special process.

[1] H. Quincke, 'Arch. f. exper. Pathol. u. Pharmakol.,' 1877, Bd. vii, S. 101.

[2] W. Jaworski, 'Deutsche med. Wochenschr.,' 1887, No. 36.

Acidum Tartaricum, tartaric acid, $C_4H_6O_6$, or $(CH)_2(OH)_2(COOH)_2$. This acid is known under four different forms. The pharmacopœial or ordinary tartaric acid is prepared from an impure acid tartrate of potassium deposited from grape-juice in the act of fermentation. It turns the plane of polarisation to the right, and consists of colourless translucent crystals, which do not change on exposure to the air. They evolve, when heated, an odour of burnt sugar, and are soluble in 0·6 part of water, and in 2·5 of rectified spirit. It is included in the German Pharmacopœia for the preparation of effervescing powders, and of potassium tartrate, to which I shall hereafter refer.

Acidum Citricum, citric acid, $C_6H_8O_7+H_2O$, or $(CH_2)_2COH.(COOH)_3+H_2O$, consists of large, colourless, translucent crystals, which decompose when slightly heated. They are soluble in 0·54 part of water, 1 part of alcohol, and in about 50 parts of ether.

Both citric acid and fresh lemon juice were formerly used in diseases caused by local or general infection, such as scurvy and articular rheumatism, and even malaria.[1] Fresh lemon juice was applied externally in micro-parasitic disorders. Citric acid has been found[2] to possess antiseptic properties, though not in a very marked degree.

The fact must not be overlooked that these vegetable acids, taken in a free state into the stomach,[3] will render the urine acid, for they are then far less easily oxidised in the system than when in the form of neutral salts. When administered in the latter form they usually render the urine alkaline.

One other vegetable acid is officinal, though it is only an impure preparation. This is agaric acid, the chief constituent of Agaricin. The acid itself is homologous with malic acid, $C_4H_6O_5$; its chemical formula is $C_{16}H_{30}O_5+H_2O$, and it is dibasic. Agaricin is obtained from the *Polyporus officinalis*, or *Agaricus albus*. This fungus grows on the stems of larches; hence the name *Fungus* or *Boletus laricis*,

[1] Maglieri, 'Fortschr. d. Med.,' 1883, S. 229.

[2] Hugo Schulz, 'Deutsche med. Wochenschr.,' 1883, S. 398.

[3] Buchheim, 'Arch. f. physiol. Heilk.,' 1857, S. 122; F. Heiss, 'Zeitschr. f. Biologie,' 1876, Bd. xii, S. 151.

by which it is sometimes known. It is imported chiefly from Archangel, in Russia.

White agaric has been used as an aperient, from ancient times. It contains resinous acids, which have an irritant effect upon the intestine. In the middle of the last century de Haën, physician to the Vienna clinic, called attention to its efficacy in checking the profuse perspirations of pulmonary phthisis. Until recently it was officinal in Germany, but was then declared to be inert, and was no longer used. Some years ago, Mannkopff of Marburg reported a case in which the *Boletus laricis* was efficacious, after atropine had been tried in vain, in checking perspirations. In 1882 a Scotchman, J. M. Young, recommended agaricin, which had then been obtained by a chemical process, for this purpose, and its effects were subsequently tested in several hospitals.[1] In the medical clinic at Bonn the chief results arrived at were as follows. Its action is beneficial, but does not set in till some hours after its administration, and very quickly passes off. The patient soon becomes tolerant of its use, so that comparatively large doses may be required to produce the desired effect.

For children the proper dose is from 0·002 to 0·008 gramme ($\frac{1}{300}$ to $\frac{1}{75}$ of a grain); for adults from 0·02 to 0·03 gramme ($\frac{3}{10}$ to $\frac{2}{5}$ of a grain). It is well not to exceed 0·005 gramme ($\frac{1}{25}$ of a grain) at first. It produced no effect either in miliary tuberculosis, in sweating of the head in rickets, or in one case of unilateral sweating of the body. Neither did it in these cases set up diarrhœa. There was no perceptible change either in the pulse or respiration which could be ascribed to the agaricin, nor was the cough or sleep affected; the general condition of the patients, however, improved.

From pharmacological investigations[2] it appears that the

[1] O. Seifert, 'Wiener med. Wochenschr.,' 1883, No. 38; O. Piering, 'Prager med. Wochenschr.,' 1884, No. 31; Proebsting, 'Cbl. f. klin. Med.,' 1884, S. 89; Senator, 'Berl. klin. Wochenschr.,' 1885, No. 1; Prior und H. Zimmermann, in the Doctordissertation of the latter, Bonn, 1887.

[2] F. Hofmeister, 'Arch. f. exper. Path. u. Pharmak.,' 1888, Bd. xxv, S. 189.

neutral salts formed by agaric acid with the alkalies, readily dissolve in water, but are soon decomposed, free acid being liberated and a basic salt formed. If agaric acid is given to kittens, it effectually suppresses the sweating of the paws due to warmth. The remedy acts directly upon the sweat-glands, not upon the nerve-centres. With this exception, agaric acid and atropine have no action in common. Diarrhœa and vomiting are set up by large doses, and death results from paralysis of the nervous centres.

The AGARICIN which is officinal in Germany is a white powder, with a feeble odour and taste, and is not readily soluble in water. In hot water it first swells up, and then forms a somewhat cloudy liquid having a slightly acid reaction. It is soluble in 130 parts of rectified spirit. The maximum single dose is 0·1 gramme (1½ grains); the maximum amount that may be given in one day has not been definitely fixed.

XXVII.

Evacuants—Tartar emetic—Some other antimonial preparations—Ipecacuanha—Apomorphine—Senega root and Quillaia bark—Purgatives—Epsom salts, Glauber's salts, the tartrates, and sulphur.

TARTARUS STIBIATUS, the best known of all the emetics, is, as may be inferred from its extraordinary name,[1] a chemical product of ancient date. It was first prepared about the year 1640 by Hadrian von Mynsicht, physician in ordinary to the Herzog of Schwerin, after the "aqua benedicta" of M. Ruland, the chief ingredient of which was tartrated antimony, had acquired a certain celebrity about the middle of the sixteenth century. The powerful action of tartar emetic on the human subject soon brought it prominently into notice, and it has remained in use ever since. It consists of colourless, transparent crystals, or of a crystalline powder, gradually efflorescing on exposure to the air; soluble in seventeen parts of cold and three of boiling water, insoluble in rectified spirit. It crepitates and blackens upon the application of heat. The aqueous solution has a slightly acid reaction, and a nauseous, sweetish taste.

Antimonium Tartartum, tartarated antimony, or Antimonii or Potassii Tartras, as we find it called in the older pharmacopœias, is an oxytartrate of antimony, and is prepared from antimonious oxide, Sb_2O_3, and purified cream of tartar or potassium bitartrate—the tartarus of the alchemists. The compound thus formed may most conveniently be regarded as consisting of two molecules of tartaric acid, $C_4H_6O_6$, in which two atoms of hydrogen have been replaced by two of the monatomic radical SbO, and two other atoms

[1] Tartarus was the name given by the Christian alchemists to all precipitates, hell (Tartarus) being regarded in the cosmography of their time as the precipitated or lowest part of creation.

of hydrogen by two of potassium. In addition, the double molecule contains one molecule of water, which results from the combination of Sb_2O_3 with $2KC_4H_5O_6$. We thus arrive at—

$$(SbO)KC_4H_4O_6 + \tfrac{1}{2}H_2O,$$

the composition of a molecule of tartar emetic.

If 0·1 to 0·2 gramme (1½ to 3 grains) of this salt is swallowed by a healthy adult, violent vomiting will be produced in from ten to twenty minutes. If a dose of only 0·03 gramme (about half a grain) is given, and repeated at intervals of fifteen minutes, vomiting will be induced in about an hour and three quarters.[1] For about half an hour before vomiting a strong feeling of nausea is experienced, which increases until vomiting takes place, and then abates to some extent, returning after a while, and generally ending with a fresh attack of vomiting. In most cases there is a feeling of chilliness and general discomfort. The rapidity, violence, and duration of the action of the drug vary greatly in different individuals. Other symptoms accompanying the stage of nausea and vomiting are, increased frequency of the pulse to the extent of some thirty beats a minute, increased frequency of the respiration, redness of the face, perspiration over the whole body, and coldness of the limbs. The temperature, taken in the axilla, remains unaltered.

In what way is the vomiting induced? Does the action originate in the peripheral nerves,—that is to say, does it arise from gastric irritation—or from stimulation of the vomiting centre[2] in the medulla oblongata? That vomiting can be induced by reflex irritation is shown under the following conditions:—if the extremities of the glosso-pharyngeal nerve are irritated by gently tickling the fauces with the finger; if the common bile-duct is blocked by an impacted gall-stone, or the pelvis of the kidney by urinary deposits; if the uterus is distended by the growing embryo; or if after dividing the vagus in a dog the central portion is

[1] Th. Ackermann, 'Beobachtungen über einige physiologische Wirkungen der wichtigsten Emetica,' Rostock, 1856.

[2] Sigm. Mayer, in L. Hermann's 'Handb. d. Physiol.,' 1881, Bd. v, Theil 2, S. 434.

stimulated by the electric current. We may therefore assume that the CORROSIVE tartar emetic directly stimulates the gastric nerves, and then by reflex action calls into play those complicated muscular movements which constitute the act of vomiting. The only difference in these cases is that the stimulation from the pharynx, liver, kidneys, or uterus, travels by different paths to the nervous centre from which the emetic impulses proceed; that centre once reached, the result is the same.

This simple explanation is in apparent contradiction to the fact that vomiting can be induced by injecting tartar emetic into the circulation,[1] and that Magendie developed the muscular contractions which are associated with the act of vomiting, by injecting tartar emetic into the circulation of a dog after the stomach had been removed. It has been inferred from these experiments that the poison acts simply and solely on the nerve-centres. This conclusion, however, is inadmissible, for, in the first place, gastritis can be produced by injecting preparations of antimony either into the blood or under the skin, precisely in the same way as after injecting preparations of arsenic; and secondly, after the administration to a female patient, on one occasion, of 0·045 gramme of tartar emetic, 0·043 gramme was recovered in the vomit, and on another occasion 0·11 gramme was recovered after a dose of 0·12 gramme;[2] and thirdly, the amount required to excite vomiting must be several times larger when it is injected into the blood, than that which suffices when administered by the stomach.[3] Further, in Magendie's experiment, it must not be overlooked that the antimony may be excreted from the system by the mucous membrane of the intestines, and there set up irritation, which stimulates the nervous centre, and so develops the reflex action which culminates in vomiting. Taking all these facts into consideration, we may conclude that tartar emetic acts primarily upon the gastric nerves, but it is possible that it also has a

[1] G. Giannuzi, 'Cbl. f. d. med. Wiss.,' 1865, S. 1 und 129.

[2] Radziejewski, 'Arch. f. Anat. u. Physiol.,' 1871, S. 472.

[3] L. Hermann, "Experimentelle Untersuchungen über den Brechact," 'Arch f. d. ges. Physiol.,' 1872, Bd. v, S. 280.

direct action upon the vomiting centre in the medulla oblongata.[1]

Vomiting is produced chiefly by the simultaneous contraction of the abdominal muscles and the diaphragm, but it is also promoted by the peristaltic movements being reversed and the cardiac end of the stomach being simultaneously dilated, the latter resulting from contractions of the non-striated muscular fibres which run from the lower end of the œsophagus, and extend about 5 or 6 cm. (about 2 inches) along the wall of the stomach. Vomiting is ordinarily induced with a view to the expulsion either of foreign bodies, or poisons, or ill-digested food (the *saburræ* of the ancients) or other contents from the stomach; and it is also employed to dislodge gall-stones, and to expel the bile, the flow of which has been prevented by their presence in the ducts. Under normal conditions very slight pressure is sufficient to cause the bile to pass into the duodenum, but the flow is easily prevented by any slight obstruction, and the bile is then absorbed into the blood, and produces jaundice. In the act of vomiting the liver is strongly compressed by the abdominal muscles and the diaphragm, and in this way the obstruction may be overcome. It is less easy to explain how it is that an emetic renders the mucus less viscid, and promotes its expulsion from the air-passages. This cannot be the direct effect of the vomiting, for during this act the epiglottis rests firmly on the top of the larynx, and it is only after the violent contraction of the abdominal muscles is lessened that it is possible for anything to pass out of the air-passages. From my own observation I am inclined to think that the emetic renders the mucus less viscid by inducing a more copious secretion of watery matter into the air-passages, that this is then dislodged in the bronchi by the thoracic movements which accompany the act of vomiting, and is then readily expelled during the attacks of coughing which quickly follow.

No explanation can be given of the fact, gained from

[1] Cf. also A. Grimm, 'Arch. f. d. ges. Physiol.,' 1871, Bd. iv, S. 205; L. Thumas, 'Arch. f. pathol. Anat.,' 1891, Bd. cxxiii, S. 44; E. Schütz, "Ueber die Einwirkung von Arzneistoffen auf die Magenbewegungen," 'Arch. f. exper. Path. u. Pharmakol.,' 1886, Bd. xxi, S. 341.

clinical observation, that inflammatory processes in the upper air-passages can be cut short by an active emetic. This has been observed in benign forms of angina, in commencing laryngitis with threatened œdema, and in similar disorders. The emetic rapidly produces its beneficial effect, —its "resolvent" or "revulsive" effect, as it was termed in former days,—but how this is brought about is a point still wrapped in obscurity.

I just now referred tò the action of tartar emetic on the mucous membrane of the air-passages. This leads me to discuss briefly here two other preparations of antimony which are officinal.

STIBIUM SULPHURATUM AURANTIACUM, Antimonium Sulphuratum, sulphuretted antimony, the so-called golden sulphide, is a fine orange-red, odourless powder. If heated in a test-tube the sulphur sublimes, leaving a residue of black sulphide of antimony or, in other words, the antimonic sulphide, Sb_2S_5, is resolved into antimonious sulphide, Sb_2S_3, and sulphur. Sulphuretted antimony is insoluble both in water and alcohol. That it is nevertheless partly dissolved by the gastric or intestinal juices is evident from the fact, that antimony has been found in the milk of a goat to which, in one experiment, a dose of 0·35 gramme of the sulphide was given, and in a subsequent experiment 1 gramme.[1] On the first occasion nine days, and on the second occasion three days elapsed before the antimony could be detected in the milk. Its presence could then be demonstrated for five days afterwards. When tartar emetic was given antimony appeared much sooner in the milk, but was present for a very short time only.

The golden sulphide of antimony, in doses of 0·03 to 1 gramme (½ grain to 1½ grains) was employed in former days —more largely than at present—as a mild "expectorant" to render ropy mucus less viscid, and to alleviate violent attacks of coughing. How it acts in these respects we cannot tell.

STIBIUM SULPHURATUM NIGRUM, black antimony, or antimonious sulphide, Sb_2S_3, which crystallises in striated masses, is still used in veterinary therapeutics. Combined

[1] G. Lewald, loc. cit., p. 20.

with a variable proportion of Sb_2O_3 it forms the *kermes mineral* of the old chemists. It no longer appears as a pharmacopœial preparation.

Tartar emetic is officinal also in the form of VINUM STIBIATUM, or antimonial wine, a clear yellowish-brown liquid consisting of 1 part of tartrated antimony dissolved in 250 parts of sherry. Owing to its taste it is readily taken by children, the dose varying from 5 to 30 drops, according to their age and the purpose for which it is administered.

There is also the UNGUENTUM TARTARI STIBIATI, the ointment of tartrated antimony, prepared with 1 part of the salt and 4 parts of vaseline. If rubbed into the sound skin it sets up eczema and ulceration of the part.

The maximum single dose of tartar emetic is 0·2 gramme (3 grains), and 0·5 gramme (7½ grains) is the largest amount that should be given within twenty-four hours.

If the dose be somewhat too large, tartar emetic occasions diarrhœa and gastric disorder, which continue after the vomiting has ceased. Here we have presented to us some of the POISONOUS EFFECTS of the remedy. They are frequently observed in the human subject, and have been exhaustively studied in animals. I have already explained to you that the effects are substantially the same as those produced by arsenious acid, the only distinction being that when given in equal quantities the effects of tartar emetic are less marked. There are a few points to which special reference may be made.

C. Mayerhofer,[1] and subsequently A. Nobiling experimented upon themselves with it, taking small doses, 0·01 to 0·03 gramme (⅐ to ½ grain) at a time, for a lengthened period. The result, as might have been anticipated, was gastritis and all its attendant symptoms. The latter writer states, "On the two subsequent days I was unable to continue the experiment, and on both these days I felt extremely feeble and depressed. My eyes sank in their sockets, and were encircled with dark rings; only for short intervals was I free from headache." In spite of these effects he proceeded with his

[1] C. Mayerhofer, 'Arch. f. physiol. u. pathol. Chemie u. Mikroskopie,' von J. F. Heller, 1846, S. 97; Nobiling, 'Zeitschr. f. Biologie,' 1868, Bd. iv, S. 40.

investigation. He injected 0·01 gramme (about $\frac{1}{7}$ of a grain) of tartar emetic dissolved in 0·5 c.c. ($7\frac{1}{2}$ minims) of water into one of the veins of his arm. "The syringe was scarcely empty," he says, "before I was seized with intense headache, there were bright flashes before my eyes, burning heat in the face, and a feeling of great fulness in the brain; I immediately suffered from severe precordial anxiety and shortness of breath, everything was dark before my eyes, I turned giddy, was forced to sit down, and after great straining, vomited some green masses. . . . Throughout the day I felt very weak, as if after recovery from a severe illness." Precisely the same symptoms were produced by the subcutaneous injection of 0·03 gramme of tartar emetic diluted with 1·25 c.c. of water into the forearm. There were also acute smarting pain and marked redness about the puncture. The writer discontinued his experiments on the seventeenth day, when albuminuria set in. This lasted for two days, together with pains in the head and stomach and a coated tongue. The dyspeptic troubles remained for two months, and the loss of weight during the seventeen days of the experiment amounted to 3·5 kilos. (about 7 lbs. 11 oz.).

I have only to add that among the other effects produced in animals, are fatty degeneration of the glands and of the heart, hæmorrhage from the capillaries, and increased albuminous waste, as measured by the nitrogen excreted in the urine, in order to complete the description of the pernicious action of tartar emetic and other soluble preparations of antimony when administered internally.

The number of cases of poisoning on record, resulting from the practice, formerly common, of giving tartar emetic to induce vomiting or allay inflammation is by no means small. The following are only a few examples:[1]

A man of thirty, died ten hours after the administration of 4 grammes (60 grains), notwithstanding the application of every means to counteract the effect of the drug; 2·5 grammes (38 grains) proved fatal in five days, 2·4 grammes (36 grains) in three. Two children died, each after a dose of 0·3 gramme (about $4\frac{1}{2}$ grains); two others, each in an

[1] Sonnenschein, loc. cit., S. 109; cf. also Mayerhofer, loc. cit., S. 100.

hour's time after taking 0·045 gramme ($\frac{2}{3}$ of a grain). A dose of 1 gramme (15 grains) developed symptoms resembling cholera, which yielded, however, to appropriate treatment. On the other hand, there are many instances in which doses quite as large have been given without producing any injurious results. The reason probably was that the greater part of the poison was rejected by the vomiting which immediately supervened.

In cases of poisoning from antimony, if the patient is seen soon after taking the dose, tannic acid is the best remedy to administer; for if to a solution of tartar emetic I add a solution of tannic acid, you will see that a copious precipitate is immediately thrown down, which does not dissolve in dilute hydrochloric acid. The danger of its absorption by the stomach is thus diminished. The fauces should be irritated with the finger or a feather, before and after giving the tannin, in order to induce vomiting. If once the preparation has passed into the circulation chemical antidotes are no longer useful. Morphia, ice, mucilaginous drinks, may be given to lessen the pain caused by the gastritis; these, together with warmth and gentle stimulants, are the only remedies which can be of any service.

Radix Ipecacuanhæ, ipecacuanha root, is also used as an emetic. It is the dried root of the *Psychotria ipecacuanha* (*Cephaëlis ipecacuanha*), a dwarf species of the Rubiaceæ growing in Brazil, and consists of more or less twisted pieces, usually about 15 cm. (6 inches) long, in the middle at most 5 mm. ($\frac{1}{5}$ of an inch) in width, and thinner at both ends, grey or brownish grey in colour, and twisted into fairly regular coils. It has a somewhat nauseous and bitter taste. A French physician, Le Gras, first brought the drug to France from Brazil in 1672, but it did not become known till 1686, when the Dauphin was successfully treated with the new remedy against dysentery, and Helvetius then sold the secret for 1000 louis d'or to Louis XIV.[1]

Powdered ipecacuanha given in doses of from 0·5 to 2 grammes ($7\frac{1}{2}$ to 30 grains) to adults, induces vomiting. Its action differs in some respects from that of tartar emetic; the antecedent retching is usually less violent, the vomiting

[1] H. Haeser, 'Geschichte der Medicin,' ii, Aufl. 1, S. 636.

recurs less frequently, the resulting collapse is less severe, and generally there is no diarrhœa.

The active principle of ipecacuanha is EMETINE. It is an alkaloid, the composition of which is not yet settled, and forms salts which do not readily crystallise, and which decompose on exposure to the air, forming a dry yellow mass.[1] It has a highly irritant action on human tissues, so much so that when large quantities of the ipecacuanha root are being reduced to powder, the faces of those engaged in the operation must be protected, as otherwise the fine dust would set up inflammation of the skin. Some people are so susceptible to it, that even the smallest quantity of the dust will occasion temporary defects of vision, or violent bronchial catarrh and asthma.[2] The pungent nature of this substance seems to be the immediate cause of the vomiting, which consequently results from direct irritation of the gastric nerves, for vomiting is not induced more quickly by injecting emetine subcutaneously or into a vein, than when given by the mouth; in whatever way it is administered to animals it gives rise to inflammation of the intestines with serous exudation, desquamation of the epithelium, the discharge of mucus, pus, and blood, and the development of ulceration. This proves that the intestinal glands are to some extent specially affected by it, in the same way as by arsenic, and that the symptoms cannot be explained as being simply due to paralysis of the vessels.

We must, nevertheless, observe that emetine speedily paralyses the nerve-centres if given in sufficient quantity. If 0·1 gramme be subcutaneously injected into a cat, death takes place in the course of fifteen or twenty minutes without any vomiting. The animal becomes weak, falls on its side, and expires "with very slight convulsions consequent on paralysis of the heart," and—it must be added—with simultaneous paralysis of the nervous centres; for if the heart were alone affected the fatal result would be attended by violent asphyxial convulsions.

Ipecacuanha is regarded as an uncertain emetic, and is

[1] von Podwyssotzki, "Beiträge zur Kenntniss des Emetins," 'Arch. f. exper. Path. u. Pharmak.,' 1879, Bd. xi, S. 231.

[2] O. Thamhayn, 'Journ. f. Pharmakodynamik,' 1857, Bd. i, S. 397.

therefore almost invariably prescribed in conjunction with tartar emetic. It is possible that this may arise from the varying amount of the active principle which is contained in the root.

The nature and value of the emetic properties of ipecacuanha are tolerably clear, but its ANTIDYSENTERIC action is not so easily understood. From the date of its discovery down to the present time [1] it has been regarded as a useful remedy in dysentery, and in Germany its value in this respect has been pointed out by no less an authority than Leibnitz, as appears from the title of his work on the subject.[2] Even at the present day Radix Antidysenterica is the name frequently given to the root. It is said to be especially beneficial in the acute dysentery of the tropics. A full dose of opium is first administered, to prevent vomiting, and then a single dose of 1·8 grammes (27 grains) of ipecacuanha, on an empty stomach.

In smaller doses, frequently repeated, ipecacuanha acts as an EXPECTORANT. In inflammation of the bronchial mucous membrane, when the secretion is dry or viscid, ipecacuanha renders the secretion more fluid, without inducing vomiting or nausea. The mucous membrane becomes less tense, the irritation which induces cough subsides, and after copious and free expectoration the general condition of the patient is improved.

The theory that emetine promoted secretion was confirmed by Rossbach's experiments, and I shall refer to this point again in speaking of apomorphine. As regards the administration of ipecacuanha, Rossbach is of opinion that the dose generally prescribed is insufficient for the above purpose, the quantity of emetine—of which the root only contains 1 per cent.—being too small to produce any appreciable result.

A more important remedy than either of the old emetics above mentioned is—

[1] A. Woodhull, 'Studies in the Non-emetic Use of Ipecacuanha,' Philadelphia, 1876, 115 pp., 8; L. Brunton, loc. cit., 1887, p. 950.

[2] "Relatio ad inclyt. soc. Leopold. nat. curios. de novo Antidysenterico americano magnis successibus comprobato," Hanover, 1696, 'Op. Omn.,' Geneva, 1768, ii, 2, 110.

Apomorphinum Hydrochloricum, hydrochlorate of apomorphine. This is a dry, white or greyish-white, crystalline powder, with a neutral reaction, soluble in forty parts of water, but almost insoluble in either ether or chloroform. If exposed to the light in a damp atmosphere it soon turns green; the fresh aqueous solution should be colourless. This compound was obtained by Mattheisen and Wright in 1869 by heating morphine and strong hydrochloric acid together in a sealed glass tube. It is morphia *minus* water, $C_{17}H_{19}NO_3 - H_2O = C_{17}H_{17}NO_2$.

The preparation was first used by Dr. S. Gee[1] in London, and it was soon after reported favourably upon in all quarters. A dose of 0·01 gramme ($\frac{1}{6}$ of a grain) in 1 c.c. (15 minims) of water, administered subcutaneously to an adult, induces free vomiting, without unnecessary discomfort, within six or eight minutes. If I inject the tenth part of that amount, 0·001 gramme, under the skin of a small dog, vomiting will take place within three minutes at the latest.

It is by no means surprising that a substance so closely allied to morphine should possess an emetic action, since morphine itself is very apt to cause vomiting; and, on the other hand, after apomorphine has been administered as an emetic, it frequently causes transient drowsiness. The effects of the two remedies are, however, in inverse proportion to each other. The first stage in the action of a full dose of morphine is marked by evidences of stimulation of the nervous centres in connection with the motor and sensory regions, such as vomiting, increased respiration, and stimulation of the mental faculties; under the influence of apomorphine this stage is much more marked. But, on the other hand, the primary stimulating effect of morphine is very quickly followed by paralysis or exhaustion of the nervous centres, whereas with apomorphine this secondary paralysing effect is only produced by the administration of large doses.[2]

There can be hardly any doubt as to the way in which apomorphine causes vomiting. There is no indication that the remedy produces its effect by reflex action, starting

[1] S. Gee, 'Clin. Soc. Trans.,' 1869, ii, 168.

[2] V. Siebert, 'Arch. d. Heilkunde,' 1871, S. 522; E. Harnack, 'Arch. f. exper. Path. u. Pharmakol.,' 1874, Bd. ii, S. 254.

either from the stomach, or from any of the other internal organs to which I previously referred. Such rapid stimulation of the vomiting centre by so small a dose can only result from the direct action of the remedy upon the medulla oblongata, just as nausea may be suddenly felt at the sight of disgusting objects, or as vomiting may be induced by movement in a swing, simply by the effect produced on the brain alone. Rabbits, which, as is well known, do not vomit,[1] exhibit symptoms of great discomfort and restlessness after a dose of 1 to 10 mg. ($\frac{1}{60}$ to $\frac{1}{6}$ of a grain) of apomorphine, symptoms which clearly result from irritation of the motor and sensory centres within the brain; the animals run about perpetually, gnawing incessantly, and manifesting extreme timidity, the respirations become hurried, there is dyspnœa, which is then succeeded by convulsions and death.

It is self-evident that a remedy which, when subcutaneously injected, produces no local irritation of the skin or stomach, and in the course of a few minutes causes the latter to discharge its contents, and which, moreover, in moderate doses is not injurious and occasions no discomfort in any other organ, is an extremely useful and important one. Unpleasant results, however, have followed its use. The following case occurred in Bonn.[2] A man fifty-four years of age with kyphoskoliosis came under treatment, suffering from chronic bronchial catarrh and slight emphysema. The prognosis was not regarded as unfavorable. A dose of 0·0045 gramme ($\frac{1}{15}$ of a grain) of hydrochlorate of apomorphine was administered subcutaneously near the ensiform cartilage, with a view to clearing the air-passages, and he died seven minutes afterwards from collapse, wiihout having vomited. The autopsy furnished no clue to any other cause of death, either immediate or remote. In another case[3] the subcutaneous injection of 0·008 gramme ($\frac{1}{8}$ of a grain) contained in a stale solution was followed by an alarming attack of fainting, but the danger passed off with the

[1] I once saw a rabbit vomit, the vomiting resulting from constant regurgitation of the contents of the stomach. Dissection disclosed stenosis of the pylorus from a tumour of a scirrhous character.

[2] Ungar, 'Sitzungsber. d. Niederrhein. Ges. f. Nat. u. Heilk.,' 1876, S. 262.

[3] M. Loeb, ref. 'Centralbl. f. d. med. Wiss.,' 1872, S. 720.

violent vomiting which speedily occurred. In children collapse has been known to result from the injection of 0·002 gramme ($\frac{1}{33}$ of a grain), so that special care must be exercised in administering the drug to them.

If after opening the trachea of a dog a milligramme of apomorphine or emetine is administered to it, a considerable increase is observed to take place in the secretion of mucus from the air-passages. The amount of blood in the mucous membrane undergoes no alteration, and if the afferent vessels are ligatured the increase in the secretion is not altogether prevented. It is evident, therefore, that the augmented secretion cannot result from an increased blood-supply. We must also exclude any action upon the glands emanating from the nervous centres, for after section of all the laryngo-tracheal nerves, and separation of the trachea both above and below, the action of the two alkaloids was still noticeable. The alkaloids, therefore, must act either directly upon the glandular tissue, the nerve-endings, or on the peripheral ganglia.[1] These experiments supplied a scientific explanation of the fact, gained by clinical experience, that use of apomorphine renders the expectoration less tenacious and makes it looser, results which had already been noted by various observers.[2]

"In every case," we are told, "the viscid mucus which is so difficult to expectorate is altered in character, the expectoration becomes more abundant and freer. The subjective improvement of the patient corresponds with the objective improvement as determined by physical examination. The crepitations or râles, instead of being dry, sonorous, and sibilant, become moist and abundant, and finally cease." The way in which the remedy is administered for this purpose is not usually subcutaneously, but in the form of a mixture. 0·01 to 0·03 gramme ($\frac{1}{7}$ to $\frac{1}{2}$ a grain) of the hydrochlorate is dissolved in 120 grammes (4 ounces) of distilled water, and to this five drops of hydrochloric acid and 30 grammes (1 ounce) of syrup are added. A tablespoonful

[1] Rossbach, 'Festschrift Würzburg,' 1882, S. 43.

[2] Jurasz, 'Centralb. f. d. med. Wiss.,' 1874, S. 499; 'Arch. f. klin. Med.,' 1875, Bd. xvi, S. 76; Kormanx, 'Deutsche med. Wochenschr.,' 1880, S. 474; Beck, ibid., 1880, S. 156.

should be given every two hours. This is the dose for adults; for children it is proportionately smaller. The first dose often causes a feeling of nausea, which, however, is not experienced from the second.

The few drops of hydrochloric acid just mentioned render a solution of apomorphine less liable to decompose. As you see in the solution before you, which is only a few days old, it acquires a green colour, which gradually becomes black. After this change the apomorphine is less reliable in its action as an internal remedy, and is no longer innocuous when used externally. Hydrochloric acid retards, but does not quite prevent this discoloration. It is asserted that the change is not due to the action of light, but solely to the air and to the medium in which the drug is dissolved; if apomorphine is dissolved in simple syrup, and the air excluded, the solution keeps quite well.[1]

Apomorphine hydrochlorate can also be obtained in the form of minute compressed tabloids, which are very convenient for use, each containing 0·01 gramme ($\frac{1}{7}$ of a grain) of the remedy. Thus prepared, the salt undergoes no change. The tabloids dissolve quickly in 1 c.c. (15 minims) of water, and by their use the stomach may be emptied of its contents in a few minutes without causing any local irritation, and in this way death may be averted after poison has been swallowed.

I will now direct your attention to a drug which is largely employed, but of which the effects are very much the same as those of small doses of the three remedies which we have just discussed. This is Radix Senegæ, the root of *Polygala senega,* belonging to the Nat. Ord. Polygalaceæ, and growing in North America. The part used is the knotty tuberosity at the head of the root, having numerous small stems and reddish scales, and tapering below into more or less twisted or curved and branched roots, which at the thickest part are not more than 1·5 cm. ($\frac{1}{2}$ an inch) across. The root has a somewhat rancid odour, and a sour, acrid taste.

A Scotch physician, J. Tennent, observed that the Indians of Virginia used senega as an internal remedy against the

[1] H. Blaser, "Die Haltbarkeit der Apomorphinlösung," 'Archiv der Heilkunde,' 1872, S. 272.

bite of the rattlesnake, and more particularly to relieve the dyspnœa induced by the poison. In 1738 he published a description of the root under the name of Rattlesnake root, and recommended its administration in inflammatory fever, pleuro-pneumonia, dropsy, and other diseases. It has since been placed in the pharmacopœia of every country. Its active principle is a glucoside named SENEGIN, which is also found in other plants; it exists in *Saponaria officinalis*, for example, under the name of SAPONIN; and in *Agrostemma githago*, the wild corn-cockle, under the name of GITHAGIN. It is a white, amorphous powder, having a neutral reaction; it is scentless, but causes violent sneezing; its taste is at first sweetish, but the after-taste is pungent and acrid. It dissolves readily in water, and the aqueous solution, even when so dilute as 1 in 1000, yields on agitation, a copious froth, like that produced from soap.

The chemical composition of senegin or saponin has not been accurately determined, as it is not of uniform composition. Ordinary saponin is probably a compound of saponin and the acid of quillaia bark. It is to this acid that the irritant and poisonous properties of the preparation are due, for saponin itself, when pure, is tasteless, and possesses no irritant action.[1]

Von Schroff experimented upon himself with senegin, and reports that a dose of 0·02—0·2 gramme (⅓ of a grain to 3 grains) causes roughness of the palate, induces cough, and increases the secretion of the mucus from the air-passages for several hours, but has no other appreciable action.[2] Similar doses injected subcutaneously act very violently. Keppler injected subcutaneously 0·1 gramme (1½ grains), dissolved in water, into the inner surface of the thigh. The immediate results were very acute pain in the region of the puncture, and a fainting fit which lasted several minutes. Erysipelatous inflammation then ensued, accompanied with marked physical and mental depression, weak and irregular action of the heart, chilliness that developed at times into

[1] Kobert, 'Arbeiten d. pharmakol. Instit. Dorpat,' 1891, vi, S. 1—146, which contains the investigations of N. Kruskal "Ueber einige Saponinsubstanzen," and also those on *Agrostemma githago*.

[2] v. Schroff, 'Lehrbuch der Pharmakologie,' 1869, S. 391.

a rigor, photophobia, lethargy, persistent nausea, ptyalism, exophthalmos, and strabismus of one eye, marked fluctuations of temperature—a rise of 2·4° C. (4·3° F.) followed by a fall to 34·2° C. (93·5° F.)—and an increase of the pulse-rate from 70 to 100 in the minute. All these symptoms persisted for several days.[1]

Besides these experiments on the human subject, a large number have also been made on animals;[2] these are interesting from a toxicological point of view. Senegin paralyses striated muscular tissue, either when introduced through the blood or when directly applied. The muscles gradually lose their excitability, remain flaccid without any apparent external change, and there is no post-mortem rigidity. Large doses paralyse the nervous system; first the sensory nerves, and then the motor nerves in the region of the puncture are affected, and subsequently the nerve-centres.

Senega root is generally prescribed as an infusion of five to ten parts of the root in 150 parts of hot water; a table-spoonful to be taken every two hours.

SIRUPUS SENEGÆ is used for children in doses of a tea-spoonful; it contains what is soluble in water and alcohol of two parts of the root mixed with 100 parts of syrup.

Poisonous symptoms of a serious character are not likely to arise from the use of senega root, soapwort root, or the glucoside derived from them, as neither drug contains any large amount of the latter, and senegin itself is not employed medicinally. On the other hand, the seeds of the CORN-COCKLE, if mixed with wheat to any large extent, are apt to produce unpleasant results, unless the bitter, acrid taste of such contaminated bread prevents its being eaten. From experiments made on animals with the seeds of the corn-cockle,[3] no doubt exists as to their poisonous qualities.

[1] Fr. Keppler, "Die acute Saponin Vergiftung, u. s. w.,' 'Berl. klin. Wochenschr.,' 1878, No. 31; Eulenberg, 'Hypodermatische Injection der Arzneimitteln,' 1875, 3 Aufl., S. 261.

[2] Pelikan, 'Berl. klin. Wochenschr.,' 1867, No. 36. From that time there has been a series of confirmatory and exhaustive investigations down to those of Fr. Przybyszewski, 'Arch. f. exper. Path. u. Pharmak.,' 1876, Bd. v, S. 137.

[3] Viborg, bei Wibmer, loc. cit., Bd. i, S. 83; Malapert u. Bonneau, 'Vierteljahrschr. f. ger. Med.,' 1852, Bd. ii, S. 100.

Among the effects produced were inflammation of the stomach and intestines, affections of the brain and spinal cord, stupor, exhaustion, and convulsions.

Cortex Quillaiæ, quillaia, or soap-bark, is the inner bark of a tree (Nat. Ord. Rosaceæ) which grows in Chili and Peru, and has only recently been introduced.[1] It is a valuable expectorant remedy, containing a larger and more definite amount of the active glucoside than is found in senega root. The daily dose for adults is from 5 to 7 grammes (75 to 105 grains), for children half that quantity. The addition of a little morphia does not interfere with its action; no unpleasant collateral or secondary effects have been observed to follow the use of the bark. Quillaia bark is indicated in all cases in which mucus is accumulating in the chest and it is desirable to promote its free expectoration. It acts partly as an irritant, causing the patient to cough more freely, and partly by stimulating and attenuating the secretion from the mucous membrane. Corresponding with these changes we find, on listening to the chest, that if previously there was abundant crepitation this begins to diminish, and soon ceases altogether; or if the respiratory sounds were previously dry and sibilant, that they are gradually replaced by those of a moist character.[2]

The use of this bark is contra-indicated in cases complicated with gastric or intestinal ulceration, as under such conditions the active glucoside may be too rapidly absorbed.

Laxatives, purgatives, cathartics, eccoprotics, aperients, drastics—to enumerate a few of the terms which our ancestors applied to this class of remedies—may be all placed in one division, their chief use being to promote evacuations from the intestines.

[1] Kobert, 'Cbl. f. klin. Med.,' 1885, S. 505; 'Arch. f. exper. Path. u. Pharmakol.,' 1886, Bd. xxiii, S. 233.

[2] F. Goldschmidt, 'Münch. med. Wochenschr.,' 1885, No. 48.

It might naturally be supposed that the way in which this action takes place would long since have been thoroughly understood. This, however, is by no means the case. It is only in recent times, by means of pharmacological experiments, under conditions artificially developed in the human intestines, that some light has been thrown on the process, and that consequently the practical application of the remedies has been put upon a more satisfactory basis. Many points still remain indefinite and obscure. To some of these, which are of interest from a scientific point of view, I shall refer in discussing the various groups and preparations. I will now proceed to consider the saline remedies belonging to the class, which are most frequently employed.

Magnesium Sulphuricum, Magnesii Sulphas, sulphate of magnesia, or Epsom salts, $MgSO_4 + 7H_2O$, consists of minute colourless, prismatic crystals, possessing a bitter, saline taste. They are soluble in 0·8 of their weight of cold, and 0·15 of their weight of boiling water, but insoluble in rectified spirit. Sulphate of magnesia was first discovered in 1695 in the mineral waters at Epsom, and afterwards in those at Sedlitz. It was then used medicinally, and has maintained its position as a mild and cheap purgative, up to the present time. In the intestine some of the sulphuric acid combines with the salts of soda and potash, but nearly the whole of the magnesia passes through the intestines, and reappears in the evacuations (Buchheim), partly in combination with products derived from the biliary secretion. The dose of the salt is from 5 to 15 grammes (75 grains to ½ an ounce). It is fortunate that no large part of the magnesia passes into the circulation, since less than a third of the aperient dose injected into the blood will cause death by paralysing the heart and respiratory organs (Hay and others). Magnesium Sulphuricum Siccum, anhydrous magnesium sulphate, a fine white powder, is also officinal. It is used when the sulphate is prescribed as a powder or in pills, for reasons which I will explain when I discuss anhydrous sodium sulphate. Sulphate of magnesium loses, by heating, nearly 36 per cent. of water, and consequently the dried form contains only two molecules of water of crystallisation. Magnesium Citricum

Effervescens, effervescent citrate of magnesium. This consists of dry citrate of magnesium, bicarbonate of sodium, citric acid, and sugar, mixed together in the form of a coarsely granulated powder. It dissolves slowly in water with free evolution of carbonic acid, and makes a pleasant acid draught, acting as an aperient. The dose is a teaspoonful.

Magnesium sulphate is present in large quantities in the mineral waters of Püllna, Saidschütz, and Friedrichshall, especially in the first, which contains 121 grammes to 10 litres (about ℥iss in 16 ounces). The mineral water of Friedrichshall, in which magnesium sulphate (51·4 in 10 litres, or about 40 grains in 16 ounces) is mixed with sodium sulphate (62·5 in 10 litres, or about 48 grains in 16 ounces), calcium sulphate (13·4), and a large amount of sodium chloride (118·7), together with a little magnesium carbonate (5·2) and free carbonic acid (6·9), is said by v. Mering[1] to produce the following results in the human subject. It improves the appetite, has an aperient and diuretic action, and a remarkable effect upon the albuminous tissues, increasing the quantity of urea, phosphoric acid, and the double sulphates. These results were observed in experiments which extended over a period of twenty-one days.

Natrium Sulphuricum, Sodii Sulphas, sodium sulphate, or Glauber's salt, $Na_2SO_4 + 10H_2O$. This consists of colourless crystals, which are efflorescent and undergo watery fusion when heated. They are soluble in three parts of cold water, in 0·3 of water at a temperature of 33° C. (91·4° F.), and 0·4 at 100° C. (212° F.), but insoluble in rectified spirit. This salt was first prepared by the physician Joh. Rud. Glauber (born at Karlstadt in Franconia, in 1604; died at Amsterdam in 1688), by decomposing common salt with sulphuric acid, and was described by him in 1638 under the name "Sal mirabile." The taste is less unpleasant than that of magnesium sulphate; the aperient effect is much the same, as are also the dose and mode of administration.

Besides its action on the bowels, this salt has also some influence upon metabolism, at least in rabbits.[2] Three grammes of sodium sulphate, introduced into the stomach of

[1] v. Mering, 'Berl. klin. Wochenschr.,' 1880, S. 153.

[2] v. Mering und Zuntz, 'Arch. f. ges. Physiol.,' 1877, Bd. xv, S. 634.

the animal, led to an increase of 10 to 15 per cent. in the consumption of oxygen for several hours.

NATRIUM SULPHURICUM SICCUM, anhydrous sodium sulphate, is officinal, with a view to the administration of this salt in the form of powder or pills. By heating sodium sulphate at a temperature of 25° C. (77° F.) all but one molecule of the water of crystallisation is driven off, and the salt then forms a somewhat fine, light, and white powder.

As I pointed out when treating of sodium carbonate, the anhydrous salt is used for the following reason: if ordinary sodium sulphate is mixed with ammonium chloride, for example, the powder becomes moist, because these two substances combine to form salts which contain no water of crystallisation; thus:

$$Na_2SO_4.10H_2O + 2NH_4Cl = (NH_4)_2SO_4 + 2NaCl + 10H_2O.$$

Many mineral waters contain Glauber's salt, the largest quantity being present in that of Püllna, 167 grammes to 10 litres[1] (about 2 drachms in 16 ounces). It is also found in the waters of Saidschütz and Friedrichshall, in one spring at Kissingen, in those of Marienbad, Franzensbad, Elster, Tarasp, Bertrich, and Carlsbad. In the "Sprudel" of the last place it is combined with some other salts. The good effects produced by this water have led to the preparation of an artificial Carlsbad Sprudel salt, which is officinal in Germany under the name of—

SAL CAROLINUM FACTITIUM, or artificial Carlsbad salt. It consists of 44 per cent. of anhydrous sodium sulphate, 2 of potassium sulphate, 18 of sodium chloride, and 36 of sodium carbonate, finely pounded together to a dry white powder, 6 grammes of which dissolved in 1 litre of water (90 grains in 35 ounces of water) make a mineral water similar to that of the Carlsbad "Sprudel" spring. As the water from this spring has a temperature of 59° C. (138·2° F.) when it issues from the ground, there is no reason why the artificial mineral water should not also be taken whilst warm. In what way Carlsbad salt prevents the formation of gall-stones —to name one of its most characteristic effects—we cannot tell.

[1] In this, as in most other cases, the figures are quoted from the well-known tables of H. Quincke, Berlin, 1872.

The principal salts of this group, the sulphates of magnesium and sodium, have a high endosmotic equivalent, that of the former being 11·7, and of the latter 11·6; while that of sodium chloride is only 4·3, and that of sugar 7·1: that is to say, if in a cylinder, one end of which is closed by animal membrane, 1 gramme of sodium chloride is placed, and the cylinder immersed in a vessel containing water, 4·3 grammes of water will pass through the membrane into the tube, and the operation will cease; but if the tube contain the same amount of Epsom salt, 11·7 grammes of water will pass through, if Glauber's salt 11·6, if sugar 7·1, &c. Poisseuille, and after him Liebig, utilised this process to explain the way in which these salts give rise to diarrhœa. They averred that a quantity of water corresponding to the endosmotic equivalent of the salt was attracted from the blood through the intestinal wall, and that this water formed the greater part of the evacuations in diarrhœa.

A second theory,[1] based upon experiment, was that the secretions of the most diverse glands, both large and small, of the intestine are strongly stimulated by these salts and by other aperient remedies, and that a larger amount of fluid is thus poured into the intestine.

A third view is that the natural peristaltic movement of the intestines is accelerated by the irritant effect of these foreign bodies to such a degree that the chyme reaches the rectum sooner and less thoroughly digested, and is consequently of a watery consistence; but that there is no increased exudation through the coats of the intestine either from the blood or from the glands.

The experiment by which the question was settled in favour of the second theory, and of its supporters, Moreau, Vulpian, L. Brunton, and Brieger, may be briefly described as follows:

A portion of the small intestine of a narcotised dog was drawn out of the abdomen, washed out by syringing through

[1] For a full account of the literature on this subject see M. Hay, 'Journ. of Anat. and Physiol.,' 1882, vol. xvi, pp. 243—254; cf. also L. Brieger, 'Arch. f. exper. Path. u. Pharmak.,' 1878, Bd. viii, S. 355; H. Hinrichsen, 'Beitrag zur Kenntniss von der Wirkung der Abführmittel, Kiel, 1884, Doctordiss. under the direction of Edlefsen.

two small openings, and divided by four ligatures into portions of equal length (from 20 to 25 cm.). Into one of these portions 5 c.c. of a 1 in 50 solution of magnesium sulphate was injected by means of a small Wood's syringe; the intestine was replaced, and the dog, still under the influence of the narcotic, was killed after the lapse of four or five hours. Only that portion into which the injection had been made, was found to be tense from the quantity of fluid contained in it. The fluid was bright yellow, alkaline, and contained shreds of mucus which dissolved in soda and were precipitated in an excess of acetic acid; it converted starch into glucose, acquired a violet colour when treated with potash and sulphate of copper, and dissolved raw fibrin when placed in an incubator. The fluid attracted by the magnesium sulphate was thus proved to contain the true secretion of the intestine.

Finally, M. Hay[1] exhaustively confirmed the above-mentioned results, and advanced the following propositions:

Saline cathartics induce a true secretion from the intestines,—chiefly, it seems, from the small intestine, every part of which has a share in producing it, the liver and pancreas contributing very little. This secretion is not a product of osmosis, but a result of irritation by the salts. The low diffusibility of these salts prevents the absorption of the fluid thus secreted. The peristaltic action is somewhat increased.

Injection of the salts subcutaneously or into the blood has no cathartic effect.

In a recent practical work,[2] containing the results of experimental research, it is maintained, on the contrary, that the fluid which collects in the intestine after the administration of Glauber's salt is not due to increased secretion from the intestinal glands, but is simply a transudation from the

[1] M. Hay, "The Action of Saline Cathartics," 'Journ. of Anat. and Physiol.,' 1882, vol. xvi, p. 243; 1883, vol. xvii, p. 62; "The Use of Concentrated Solutions of Saline Cathartics in Dropsy," 'Lancet,' 1883, April 21st; J. Hess, 'Deutsches Arch. f. klin. Med.,' 1886, Bd. xl, S. 93; J. Brandl und H. Tappeiner, 'Arch. für exper. Path. u. Pharmak.,' 1889, Bd. xxvi, S. 177.

[2] H. Kuchanewski, "Ueber das Transudat in den Darm unter dem Einfluss der Mittelsalze," 'Arch. f. klin. Med.,' 1890, Bd. xlvii, S. 1.

intestinal blood-vessels; that owing to this transudation, and to the increased peristaltic movement of the intestines induced by the irritation of the mucous membrane, any fæcal matter which may be present is rendered less consistent, and its expulsion is accelerated.

Natrium Chloratum, sodium chloride, common salt, NaCl, is undoubtedly a very important constituent of many mineral waters, and especially of those in which it is, whether in conjunction or not with sodium bicarbonate and other salts, the principal saline ingredient.

It consists of white cubes, or of a crystalline powder. It is soluble in 2·7 parts of water, and has a neutral reaction. As to its mode of action on the system very little explanation has as yet been offered. The following are some of the results which have been obtained by experimental research.

Owing to its physical properties it accelerates osmosis in the tissues, and so increases the albuminous waste and consequently the amount of urea excreted from the system. To eliminate the salt in the urine requires an increase in the aqueous constituent of the latter; this water is abstracted from that which would otherwise be exhaled from the lungs, and if that is not sufficient some is abstracted from other organs. Common salt thus acts as a diuretic.[1] It also increases the production of lymph in the tissues and promotes its circulation.[2]

A small quantity of sodium chloride added to a fermenting mixture of yeast and sugar increases the activity of the yeast cells.[3] It also increases the action outside the body of such unorganised ferments as ptyalin, trypsin, and diastase,[4] and of pepsin upon fibrin.[5] Large quantities, of course, interfere with any such fermentative action.

It promotes the secretion of pepsin. If a cleansed

[1] C. Voit, "Untersuchungen über den Einfluss des Kochsalzes, u. s. w.," 1860, S. 29—66.

[2] R. Heidenhain, "Versuche und Fragen zur Lehre von der Lymphbildung," 'Arch. f. d. ges. Physiol.,' 1891, Bd. xlix, S. 208.

[3] J. v. Liebig, "Ueber Gärung, u. s. w." ('On Fermentation, &c.'), 1870, S. 61.

[4] O. Nasse, 'Arch. f. d. ges. Physiol.,' 1875, Bd. xi, S. 151.

[5] L. Wolberg, ibid., 1880, Bd. xxii, S. 297.

pylorus is treated with glycerine the resulting extract is usually very weak, and contains little pepsin; but if the pylorus is treated with a solution of sodium chloride the resulting solution is much more active. If sodium chloride produces the same effect within the body, then those mucous membranes in which pepsin is most abundant ought also to contain the largest amount of this salt. As a matter of fact, the amount of sodium chloride in dried mucous membrane has been proved by a series of experients to vary from 0·62 to 1·5 per cent., the larger amounts being found where the chief cells were large and clear, and contained an abundant supply of pepsin. If a full dose (10 grammes) of sodium chloride is injected into the veins of a fasting dog the secretion of pepsin takes place more rapidly, so that in an hour afterwards the mucous membrane is always thinner than in the control animal.[1]

We will now consider the various salts belonging to this class of remedies.

KALIUM ACETICUM, Potassii Acetas, acetate of potassium, $KC_2H_3O_2$. A white deliquescent salt, soluble in 0·36 of its weight of water or in 1·4 of alcohol. It slowly turns red litmus paper blue, is converted into a carbonate in the body, renders the urine alkaline, or at all events less acid, and increases its amount.[2] It is used in enlargements of the spleen and liver, and in cases of gout and dropsy. As it is very deliquescent the salt itself is rarely prescribed, but it is ordered in the form of LIQUOR KALII ACETICI, or solution of acetate of potassium, which is officinal in Germany. This preparation consists of 1 part of the salt and 2 of water, and is added to mixtures in the proportion of about 20 parts to 150.

The four next salts contain tartaric acid.

KALIUM TARTARICUM, Potassii Tartras, tartrate of potassium, consists of colourless, transparent crystals which are unaffected by the atmosphere, and form a neutral solution

[1] For information upon the action of salts see also F. Hofmeister, 'Arch. f. exper. Path. u. Pharmak.,' 1887, Bd. xxiv, S. 247; 1888, Bd. xxv, S. 1.

[2] R. v. Limbeck, "Ueber die diuretische Wirkung der Salze," 'Arch. f. exper. Path. u. Pharmak.,' 1888, Bd. xxv, S. 69.

with 1·4 parts of water, but are very slightly soluble in alcohol. Its formula is $(K_2C_4H_4O_6)_2+H_2O$. It has a mildly cathartic action, and formerly stood in high repute as a so-called "resolvent" for enlargements of the spleen and liver. Like the preceding salt, it is transformed in the body into potassium carbonate, a change which also takes place in aqueous solutions if they are kept for some time. Nothing more is known of its properties from a physiological point of view. It is given in doses of 1 to 5 grammes (15 to 75 grains) two or three times a day.

Kalium Bitartaricum, Potassii Tartras Acida, the Tartarus Depuratus of the German Pharmacopœia, acid tartrate of potassium, is a white, crystalline, gritty powder, of a pleasant acid taste, soluble in 192 parts of cold and 20 of hot water, insoluble in rectified spirit, but readily soluble in a solution of caustic soda, and dissolving with effervescence in a solution of carbonate of potassium. Its composition is $KC_4H_5O_6$. Many wines, when kept, deposit this salt, together with calcium tartrate and colouring matter, as a crust on the sides of the cask. This salt is purified and separated from the other products, and is then commonly known under the name of Cremor Tartari, or cream of tartar. The conversion of the salt into carbonate, which begins even in the intestines (Buchheim), may have a useful effect indirectly in various disorders. In England it is prescribed in gout and for renal calculus, and may possibly render the uric acid more soluble. It increases the secretion of urine, and as a diuretic is prescribed in small doses, 0·2 to 0·5 gramme (3 to 7½ grains), several times a day. It produces watery evacuations from the bowels without causing any great intestinal irritation, and for this purpose is given in doses of 5 grammes (75 grains) and upwards.

Kalio-natrium Tartaricum, Tartarus Natronatus, Soda Tartarata, tartarated soda. This consists of colourless, transparent, crystalline prisms, which are soluble in 1·4 parts of water and form a neutral solution. As long ago as 1672 this salt was sold by Seignette as a secret remedy at Rochelle, hence the origin of the two names by which it is known at the present day. Its formula is—

$$KNaC_4H_4O_6+4H_2O.$$

It is readily soluble in water, and given in doses of from 5 grammes to 10 grammes (75 to 150 grains) acts as a mild purgative. Small doses frequently repeated appear to have a diuretic action. It is also said to have a slightly stimulating effect on the biliary secretion.[1] Tartarated soda is one of the ingredients of PULVIS AËROPHORUS LAXANS, Seidlitz powder, in which 7·5 grammes (113 grains) of it are combined with 2·5 grammes (38 grains) of bicarbonate of sodium and 2 grammes (30 grains) of tartaric acid. The first two salts are mixed together and dispensed in blue paper, and the acid in a white paper.

KALIUM TARTARICUM BORAXATUM, the TARTARUS BORAXATUS of the German Pharmacopœia, or soluble cream of tartar, is a white, amorphous, deliquescent powder, with an acid taste and reaction, soluble in its own weight of water. It is prepared by dissolving 2 parts of borax with 5 of purified cream of tartar, and is prescribed in doses of from 0·5 to 1 gramme (7½ to 15 grains) as a diuretic. Solutions of this salt readily decompose and become mouldy, the cream of tartar being precipitated.

KALIUM BICARBONICUM, bicarbonate of potassium, $KHCO_3$, dissolves slowly in 4 parts of water, forming an alkaline solution, but is insoluble in rectified spirit. It may be employed for the same purposes as the preceding salt (which in the body is transformed into the carbonate), or for those which I have already enumerated when discussing the corresponding sodium salt.

In this group we may include PULPA TAMARINDORUM, tamarind pulp, which is officinal both in the crude and purified state. The former preparation is the dark brown pulp freed from the shell or epicarp of *Tamarindus indica*, a leguminous plant which grows in tropical Asia and Africa and attains the height of 25 metres (about 80 feet); the latter is the same pulp freed from its tough fibres, the seeds, and their membranous coats, and from fragments of rind, by being soaked in water and then rubbed through a hair-sieve. It has a pleasant acid flavour, due to the tartaric and citric acids contained in it, either in a free state or combined with potash, and to the sugar. In twenty-

[1] Rutherford, loc. cit., p. 193.

one specimens of East Indian tamarinds which were analysed, the average composition was, in round numbers,—water 25, sugar 18, cream of tartar 5, tartaric acid 7, and citric acid 2 per cent., the remainder being made up of immaterial vegetable substances.[1] Tamarind pulp is prescribed in doses varying from a teaspoonful to as much as will lie on the end of a knife; or as a hot infusion containing from 50 to 100 parts in 200 to 500 parts of water. The amount to be taken varies considerably according to circumstances.

A special place is reserved among cathartic medicines for SULPHUR. It is used medicinally in three forms—SULPHUR Sublimatum, Depuratum, and Præcipitatum.

SULPHUR SUBLIMATUM should, when volatilised by heat, not leave more than 1 per cent. residue. It frequently contains some arsenic. Well washed with water and ammonia —the latter dissolving the arsenious sulphides and arsenious acid—it yields SULPHUR DEPURATUM, a dry, yellow powder, without taste or smell.

SULPHUR PRÆCIPITATUM, precipitated sulphur, milk of sulphur, is prepared from the alkaline or earthly sulphides by dissolving them in water, and precipitating the sulphur by means of an acid. It is a fine, yellowish-white powder, not crystalline.

Buchheim states that no particular results were noticed after the administration to a young man[2] in one day of upwards of 22·3 grammes (about 5½ drachms) of sulphur, except that the evacuations were softened, and that these and the flatus had an offensive odour, and that there was a certain amount of colic. The appetite was undisturbed. As much as 46 per cent. of the finely divided milk of sulphur, oxidised into sulphuric acid, was afterwards detected in the urine; but on an average only 15 per cent. of the purified sublimed sulphur (flowers of sulphur) was eliminated in this way.

If sulphur is given to animals for some time, their perspiration and breath have the odour of sulphuretted hydro-

[1] H. Brunner, ref. im 'Chem. Repertorium,' 1891, S. 34 (Beilage der Chemiker-Zeitung).

[2] H. Krause, 'De transitu sulphuris in urinam,' Doctordiss., Dorpat, 1853.

gen; and in the human subject, if sulphur is taken in sufficient quantity to act as a cathartic, silver articles worn on the person turn black, owing to the formation of silver sulphide.

7·772 grammes of dry sulphur were given to a dog in a state of nitrogenous equilibrium. 0·374 gramme, or 5 per cent., was excreted in the urine, the remainder in the fæces. In an experiment on another animal, out of 4·676 grammes of sulphur, 0·471, that is 10 per cent., passed off by the urine.[1]

Experiments outside the body prove that sulphur is readily converted into sulphuretted hydrogen, by the action of decomposing albuminoid substances, and that this gas, in the presence of alkaline carbonates or basic phosphates, is converted into an alkaline sulphide. This is the form in which sulphur would probably, to some extent, be found in the small intestine, and this alkaline sulphide, when carried in the circulation to the skin, would there be decomposed by the acid secretions, and exhaled as sulphuretted hydrogen. The flesh of animals to which sulphur has been given for some time, smells and tastes of sulphuretted hydrogen, which is liberated from the alkaline sulphide by the acids which are generated when rigor mortis sets in. A large portion of the alkaline sulphide combines with oxygen in the body, and forms, according to Voit and Regensburger, sulphuric and hyposulphuric acids, which—combined, of course, with bases—are subsequently found in the urine. The normal amount of sulphides in the fæces of carnivora is largely increased by adding sulphur to their food. It has no effect on the albuminous waste in the system.

A portion of the sulphur appears also[2] to pass into the urine in the form of an alkaline sulphide. A small dog had 3·6 grammes of flowers of sulphur given to it in its food; three hours later the urine was collected, mixed with hydrochloric acid and covered with a paper which had been moistened with a solution of lead acetate. At the end of twenty-

[1] M. Regensburger, "Die Ausscheidung der Schwefelsäure im Harn nach Aufnahme von feinzerteiltem Schwefel in den Darm," 'Zeitschr. f. Biologie, 1887, Bd. xii, S. 480; Hugo Schulz und Strübing, 'Deutsche med. Wochenschr.,' 1887, S. 24.

[2] Wöhler, loc. cit., p. 131.

four hours the paper had become black, owing to the liberation of sulphuretted hydrogen from the urine.

So much for our theoretical knowledge of the action of sulphur. Clinically, all that we know about it is, that in moderate doses (from 1 to 3 grammes [15 to 45 grains] of the purified substance) it stimulates the intestine and causes diarrhœa. Further, the disciples of Hippocrates administered it internally in cases of asthma,[1] and some physicians have, in recent times, again tried it in this disorder. Its action in promoting evacuations from the intestines may be due to the formation of sulphuretted hydrogen, which stimulates the nerves, and perhaps the muscular coat also, of the intestines.[2] Its action on the nervous centres may possibly be dependent upon the formation of sulphides, which have a paralysing effect on nervous tissue.[3]

As a laxative, sulphur is a constituent of the Pulvis Liquiritiæ Compositus, or Pulvis Glycyrrhizæ Compositus, a remedy which is largely used, and to which I shall refer when we discuss Folia Sennæ.

The value of the fumes of sulphur as an external disinfectant, κακῶν ἄκος,[4] has long been recognised and is indisputable. The resulting sulphurous acid acts energetically as a poison upon the lowest forms of organic life. An atmosphere impregnated with only 0·25 per cent. by volume of sulphurous acid destroys the vitality of the yeast ferment in a very short time.[5] The same effect is produced, under

[1] Dierbach, 'Die Arzneimittel des Hippokrates,' 1824, S. 240.

[2] Bokai, 'Arch. f. exper. Path. u. Pharmak.,' 1887, Bd. xxiii, S. 229.

[3] J. Pohi, ibid., 1886, Bd. xxii, S. i.

[4] Ulysses used it to cleanse the great hall after the slaughter of the suitors, Odyssey, xxii, 480—494:

"To Euryclea then addrest the king:
Bring hither fire, and hither sulphur bring,
To purge the palace. . . .
* * * * *
'Bring sulphur straight and fire' (the monarch cries).
She hears, and at the word obedient flies,
With fire and sulphur, cure of noxious fumes,
He purged the walls and blood-polluted rooms."

(Pope's translation.)

[5] G. Jüdell und Hoppe-Seyler, 'Med.-chem. Untersuchungen,' 1868, S. 417; and 1871, S. 580.

certain limitations as to time, on all microscopic germs which are found floating in the air or deposited on the various articles of furniture in rooms. The protoplasm of which these germs consist is paralysed by the sulphurous acid gas. Threads dipped in sulphur are employed for the purpose, or sulphur matches such as are used for the fumigation of wine casks in order to destroy any fungus spores that may be lodged in them; burning pieces of sulphur, the size of a hazel-nut or walnut, in a suitable apparatus, after first moistening them with alcohol,[1] is another method. It is desirable that some fresh air should be admitted to the room during the fumigation, as the sulphur soon ceases to burn if there is an insufficient supply of oxygen. Coloured materials (curtains, wall-papers, &c.) and articles made of iron (steel grates, fire-irons, &c.) are damaged by the fumes of sulphurous acid gas, just as they are when chlorine and bromine are employed as disinfecting agents.

[1] Wolffhügel, R. Koch, B. Proskauer, 'Mittheil. d. Kaiserl. Gesundheitsamtes,' 1881, Bd. i, S. 188—301.

XXVIII.

Carthartics of organic origin, with the exception of the tartrates—Anthelmintics.

We now come to a series of purely organic substances which are included among the cathartic remedies. The simplest of these, to which I will first direct your attention, is sugar of milk, SACCHARUM LACTIS, $C_{12}H_{22}O_{11}+H_2O$. It consists of greyish-white crystals, or of a white crystalline powder, soluble in 7 parts of water at a temperature of 15° C., and in 1 part of boiling water, forming a slightly sweet but not syrupy liquid. Its properties became known to us through the use of WHEY. The latter is prepared by coagulating the casein in skim-milk by means of rennet (the mucous membrane of the abomasum of the cow), and separating it from the serum or whey. It is a sweet liquid, and contains the sugar, albumen, and the greater part of the salts in the milk; the phosphates are retained by the casein. Sugar of milk has recently been recommended by M. Traube as an efficacious and agreeable laxative.[1] From 9 to 15 grammes—that is, from 3 to 5 teaspoonfuls—are dissolved in about 250 ccm. (about 8½ ounces) of boiled skim-milk, still warm, and taken in the morning an hour and a half before breakfast. It almost invariably produces one or two loose and painless evacuations a few hours afterwards. It is supposed that the increased peristaltic action is due to the conversion of the sugar of milk into lactic acid; a view which is supported by the fact that sodium lactate causes diarrhœa.

Sugar of milk also serves as a vehicle for powders, especially such as are liable to suffer chemical change in damp air if mixed with cane sugar, which, though it has a

[1] M. Traube, 'Deutsche med. Wochenschr.,' 1881, S. 113.

pleasanter taste, is more deliquescent than milk-sugar. An allied substance is—

MANNA, the concrete exudation of *Fraxinus ornus*, a tree belonging to the Nat. Ord. Oleaceæ, to the cultivation of which whole plantations in Southern Italy are devoted. The manna flows from incisions in the bark and then hardens. It consists of dry crystalline lumps, rounded, flat or concave, pale yellow outside, white inside, and has a sweet taste. Its essential ingredient is mannite, $C_6H_8(OH)_6$, a crystalline substance which is a hexatomic alcohol, and of which glucose, as an aldehyde, is a derivative. The best manna contains 60 to 80 per cent. of mannite.

This remedy is not readily tolerated when the digestive function is disordered. It is given internally in doses of from 5 to 15 grammes (75 to 225 grains), either in water or as an electuary. Dissolved in water, filtered, and boiled with sugar, it forms SIRUPUS MANNÆ, a laxative very generally prescribed for children. The dose is a teaspoonful.

This vegetable exudation takes its name from the *manna* of the East, a substance which is, however, totally different and exudes, especially in the region about Mount Sinai, from punctures made by a cochineal insect, *Coccus maniparus*, in the branches of *Tamarix gallica*, a very succulent plant, some six metres high, which grows in the valleys of the peninsula of Sinai. In summer this tamarisk manna trickles from the topmost branches in white honey-like drops, and is collected in leather bags by the Bedouins. Some of it is used by them as a condiment with their bread, some is sold at Cairo, and some goes to the monastery, where the Prior stores it up and presents it in little tin cylinders to departing pilgrims for their journey.[1] As a food, the manna of Sinai is not to be despised, for, according to an analysis made by Berthelot in 1861, the dry substance contains about 1·5 per cent. of water, nearly 55 per cent. of cane-sugar, 25 per cent. of invert-sugar, and 20 per cent. of dextrine and vegetable mucus.[2]

OLEUM RICINI, or castor oil, is another mild intestinal

[1] G. Ebers, "Durch Gosen zum Sinai," 1872, S. 224.

[2] Flückiger, loc. cit., p. 27; for references on this point, see also Ebers and Strumpf, 'Arzneimittellehre,' 1848, i, S. 175.

stimulant. It is a pale yellow, viscid liquid of peculiar taste and smell, rather lighter than water; when exposed to the air in thin layers it slowly dries up to a varnish. The oil is expressed from the seeds, the husks having been removed, of *Ricinus communis*, an East Indian plant belonging to the Nat. Ord. Euphorbiaceæ, which is also grown in Europe for ornamental purposes. It is the glyceride of ricinoleic acid, its formula being $C_3H_5(C_{18}H_{33}O_3)_3$, with some palmitin and stearin glyceride, and some cholesterin. In the intestines a portion of the castor oil is decomposed by the pancreatic ferment, the acid is liberated and acts as a stimulant on the intestinal wall, the effect, however, being modified by the presence of the undecomposed portion of the oil. The dose is from 5 to 30 grammes (a teaspoonful to two tablespoonfuls). Its employment as an aperient in Germany dates only from the beginning of the present century.

The castor-oil plant is a common ornamental shrub, and as the seeds have a pleasant appearance they are occasionally eaten. They are highly poisonous. Three or four of them if swallowed will induce violent sickness, gastric and intestinal pains, and great prostration.[1] The poisonous substance is an amorphous albuminous compound,[2] of the nature of a ferment and of neutral reaction, named ricinine. Even in small doses it will develop some of the symptoms above mentioned. An examination of the bodies of animals which had been poisoned with the seeds, showed the presence of inflammation and ulceration of the stomach and intestines. In some of the animals experimented upon, death was accompanied by convulsions, but in the majority it resulted from exhaustion whilst the animal was in a narcotised state. In experiments with the seeds of other varieties of Ricinus exactly the same effects were produced as from the seeds of *Ricinus communis*. The aperient effect of the oil is independent of the action of the ricinine.

FRUCTUS RHAMNI CATHARTICA, buckthorn berries, are round

[1] Wibmer, loc. cit., Bd. iv, S. 413; Langenfeldt, 'Berl. klin. Wochenschrift, 1882, S. 9. Sixteen simultaneous cases, see ref. 'Cbl. f. klin. Med.,' 1889, S. 37.

[2] Kobert und H. Stillmark, 'Arbeiten aus dem Pharmak. Institut zu Dorpat,' 1889, iii, S. 59.

berries about 1 cm. in diameter, the fruit of *Rhamnus cathartica*, a bush belonging to the Nat. Ord. Rhamnaceæ, which grows wild in Germany. When fresh they yield a greenish-violet juice of acid reaction, the taste of which is at first sweet and subsequently nauseating and bitter. The colour of the juice is turned greenish yellow by alkalies and red by acids. Its action on the intestines as a cathartic appears to be due to the bitter principle, an uncrystallisable substance to which the name rhamnocathartin has been given. The drug is prescribed in the form of syrup for children, in doses of a teaspoonful, but is very little used at the present day.

Another of the genus *Rhamnus*, the *Rhamnus frangula*, indigenous in Germany, is officinal in the form of—

Cortex Frangulæ, the bark of the black alder, or alder buckthorn, which consists of small quills 1·5 mm. thick and about 3 dm. long, varying in colour from dull brown to grey, and having a pleasant sweetish taste. The bark should not be given till it has been kept some time, as when fresh it contains an emetic principle. The purgative property of the bark is attributed to rhamnoxanthin, or frangulin, $C_{21}H_{20}O_9$, which when acted upon by ferments is resolved, with the absorption of water, into glucose and frangulinic acid. A few decigrammes of this acid operate as an effective purgative on dogs.[1] Cortex Rhamni Frangulæ is one of the cathartic remedies which can be taken for a long period without losing its effect or acting injuriously on the patient. It is usually prescribed in cases of habitual constipation, in combination with some ethereal oil—as, for example, Cort. Frangulæ, Semin. Fœniculi, ana 100. Ft. species. S. 1 to 2 teaspoonfuls to be infused in $\frac{1}{3}$ of a litre (12 ounces) of hot water and strained; to be taken fasting an hour before breakfast. The Extractum Frangulæ Fluidum is also officinal; the dose is from 20 to 30 drops two or three times a day.

Podophyllinum, podophyllin. The podophyllin, or resin of podophyllum, is separated by pouring the spirituous extract of the rhizome of *Podophyllum peltatum*, a North American

[1] J. Bauemker, on the authority of Husemann and Hilger, 1884, S. 895.

species of Berberis, into water. It is a yellow amorphous powder, or appears as a loose, friable, resinous substance of a yellow or brownish-grey colour. The root has long been used as a remedy by the natives, and was introduced into Europe about the year 1820. In moderate doses it stimulates the peristaltic movement of the intestine, and is also said to promote the secretion of bile; in large quantities it produces gastritis and violent diarrhœa, accompanied with intestinal hæmorrhage, and may cause death from paralysis of the nervous centres. The latter is readily induced by the subcutaneous injection of podophyllotoxin,[1] which is the most active constituent of the resin; 0·005 gramme ($\frac{1}{13}$ of a grain) thus administered is absolutely fatal to a full-grown cat. The officinal podophyllin is recommended as an aperient, though it acts slowly, in doses of 0·005—0·05 gramme ($\frac{1}{13}$ to $\frac{3}{4}$ of a grain). As a possible remedy in biliary colic, 0·01 gramme ($\frac{1}{6}$ of a grain) may be given twice daily. An alcoholic solution is used in North America as a cutaneous irritant.

Folia Sennæ, senna leaves, the leaflets of *Cassia angustifolia* and *C. acutifolia,* shrubs (Cœsalpiniæ) indigenous to the tropics. The active principle is cathartic acid, which exists in the leaves combined with lime and magnesia, these compounds being soluble in water.[2] Senna is prescribed as an infusion of 5 to 15 parts in 150 of water, of which a tablespoonful or more may be administered every two hours. When taken in sufficient quantity it causes a greenish discoloration of the urine, which, like that produced after taking rhubarb, is due to the presence of chrysophanic acid. The preparations are—

(1) Infusum Sennæ Compositum, a hot infusion of senna in which some tartarated soda and manna are dissolved. This is taken in doses of a tablespoonful, and generally takes some time to act.

(2) Electuarium e Senna, or lenitive electuary, made

[1] V. Podwyssotski, 'Arch. f. exper. Path. u. Pharmak.,' 1880, Bd. xiii, S. 29. See also a German monograph of sixty-one pages by the same author, St. Petersburg, 1881.

[2] Buchheim, confirmed by R. Stockman, 'Arch. f. exper. Path. u. Pharmak.,' 1885, Bd. xix, S. 117.

by gently heating together Folia Sennæ with Semen Coriandi, Pulpa Tamarindorum, and Sirupus Simplex, which form a greenish-brown electuary of uninviting appearance. The dose is a teaspoonful.

(3) Sirupus Sennæ. Folia Sennæ and Semen Fœniculi are digested with hot water and a little alcohol, and to the strained liquid a certain amount of sugar is added.

(4) Pulvis Liquiritiæ Compositus, or Pulvis Pectoralis Kurellæ, German liquorice powder. Notwithstanding its names, which refer to other ingredients and other effects, this is substantially a preparation of senna. It contains Radix Liquiritiæ and Folia Sennæ in equal quantity, together with Sulphur Depuratum, Semen Fœniculi, and Saccharum Album. From one to three teaspoonfuls, taken in the course of twelve hours, generally suffice to produce a mild aperient effect.

(5) Species Laxantes, aperient tea. This consists of Folia Sennæ, Flores Sambuci, Semen Anisi, Semen Fœniculi, and Kalium Bitartaricum, moistened, cut fine, pounded, and mixed. An infusion of this is prepared and taken like tea.

Radix Rhei, rhubarb root. This is the rhizome, more or less deprived of its bark, of *Rheum officinale* and other species indigenous to Central Asia, but also cultivated in Europe. Its principal constituent is a substance allied to cathartic acid, the precise nature of which, however, is not fully known; its colouring matter, chrysophanic acid, also possesses cathartic properties. It also contains tannic acid and bitter extracts. In small doses, 0·1 to 0·2 gramme (1½ to 3 grains) several times a day, rhubarb acts as a stomachic. Taken in this way it sometimes lessens the number of evacuations, owing to the action of the tannic acid and the bitter extract. In larger doses, from 0·5 to 1·5 grammes (7½ to 23 grains), it induces frequent and pultaceous evacuations, with or without colic, according to the dose and the susceptibility of the individual. The urine often acquires a greenish or—if alkaline—a red colour, similar to that produced by jaundice or by hæmaturia, from the chrysophanic acid which it contains. The addition of mineral acids, however, to the urine makes the colour brighter, which is not the case when it arises from either of the other

conditions. A similar discoloration produced by santonin, may be distinguished by this peculiarity among others, that if turned red by an alkali, it does not lose its colour on being digested with zinc powder—a reducing agent—as is the case with urine coloured by rhubarb.[1] I shall refer to this point again when treating of santonin. Rhubarb root contains a small amount of oxalate of lime, which is said to give rise to calculi in the bladder if the remedy is taken for some time. The root is given in the doses above mentioned, either in the form of powder, pills, or decoction. The preparations are—

(1) EXTRACTUM RHEI.—This is prescribed in powder or pills, in the same way as the root.

(2) EXTRACTUM RHEI COMPOSITUM.—This consists of Extractum Rhei, Extractum Aloës, Resina Jalapæ, and Sapo Medicatus. For adults the medium dose, as an aperient, is 0·3 gramme (4½ grains) as a pill. Either extract can be given as a powder.

(3) TINCTURA RHEI AQUOSA.—This is prepared by digesting Radix Rhei in water with Borax and Potassii Carbonas, and afterwards adding Spiritus and Aqua Cinnamomi. The dose is a teaspoonful.

(4) TINCTURA RHEI VINOSA.—Rheum, Cortex Fructus Aurantii, and Fructus Cardamomi are macerated in Vinum Xerense, then subjected to pressure, and sugar added to the liquid. It is a useful stomachic, the dose for this purpose being half a teaspoonful or less.

(5) SIRUPUS RHEI.—This contains, besides sugar, all the ingredients of Tinctura Rhei Aquosa except the alcohol.

(6) PULVIS MAGNESIÆ CUM RHEO—Hufeland's powder for children—contains rhubarb, carbonate of magnesia, oil of fennel, and sugar. It is given as a stomachic in small doses, from 0·1 to 0·2 gramme (1½ to 3 grains), and in larger doses as a cathartic.

TUBERA JALAPÆ, Radix Jalapæ, or jalap root. These are the pear-shaped tubercles of *Ipomæa purga*, belonging to the Nat. Ord. Convolvulaceæ, and indigenous to the Mexican Andes. The active principle in it is convolvulin, $C_{31}H_{50}O_{16}$, with a little jalapin, $C_{34}H_{56}O_{16}$, both being

[1] J. Munk, 'Arch. f. pathol. Anat.,' 1878, Bd. lxxii, S. 136.

anhydrous acids. They act on the intestines after being dissolved by the bile.[1] As a mild aperient jalap root is given in doses of about 0·3 to 0·5 gramme (4½ to 7½ grains) for adults; and in doses of double or treble that amount if required to act more strongly. A single dose of 0·3 gramme (5 grains) of calomel combined with 1 gramme (15 grains) of jalap was formerly a favourite revulsive remedy, as it was called, for inflammatory diseases when the bowels were healthy. The dose, however, was frequently rejected by the stomach.

Other preparations, which are also officinal, are:—(1) RESINA JALAPÆ, the alcoholic extract of the tubercles. The resin consists for the most part of the convolvulin or anhydrous convolvulinic acid above mentioned. In doses of 0·1 to 0·2 gramme (1½ to 3 grains) it acts as a mild aperient. It is given either in the form of powder or pills. (2) SAPO JALAPINUS. Resina Jalapæ and Sapo Medicatus rendered soft by alcohol and mixed together, and then evaporated by a water-bath to a suitable consistence for forming pills. The dose is from 0·5 to 2·0 grammes (7½ to 30 grains). (3) PILULÆ JALAPÆ. This consists of 3 parts of Sapo Jalapinus and 1 part of jalap powder mixed together, and then divided into pills each weighing 0·1 gramme (1½ grains). One to six pills may be taken as a dose.

ALOË, aloes. The inspissated dark brown resinous juice which exudes from vessels placed longitudinally between the outer green cellular layer and the inner colourless layer of the fleshy leaves, when the latter are incised transversely.

The plant, which belongs to the Nat. Ord. Liliaceæ, grows wild in hot climates. The best aloes comes from Cape Colony, and is consequently the only kind used in Germany. This consists chiefly of the active principle, aloetin (Buchheim), an amorphous substance of a chemically neutral character, which is found in other varieties in a crystalline form, and is termed Aloin.[2] Aloes is also supposed to act as a bitter tonic, and to promote digestion. It is further said to cause hyperæmia of the intestinal canal, especially

[1] G. Zwicke, 'Convolvulin und Jalapin,' Doctordiss., Halle, 1869.

[2] W. Craig, 'Edin. Med. Journ.,' 1875, May and June; ibid., 1877, April.

of the lower portion; and it is supposed to be capable, by inducing hæmorrhage, of ameliorating hæmorrhoidal obstruction, and of stimulating the catamenial flow in amenorrhœa. In inflamed conditions of the colon or rectum it may aggravate the mischief. In animals the subcutaneous injection of aloin or extract of aloes gives rise to gastro-enteritis and nephritis.[1] The dose of aloes is from 0·1 to 0·5 gramme (1½ to 7½ grains) in the form of pills, two or three times a day. In cases of suppressed menstruation it may be given as an enema. The preparations are:

(1) Extractum Aloës, the dry aqueous extract. Its action is said to cause less pain than crude aloes; dose, 0·1 to 0·3 gramme (1½ to 5 grains).

(2) Tinctura Aloës Composita, elixir ad longam vitam. Aloes with the addition of Radix Gentianæ and Radix Rhei, Rhizoma Zedoariæ and Crocus; dose, from half a teaspoonful to a teaspoonful.

(3) Pilulæ Aloëticæ Ferratæ, or Italian pills. Equal parts of aloes and dried sulphate of iron mixed together with rectified spirit and made into pills, each weighing 0·1 gramme (1½ grains). Coating the pills over with tincture of aloës gives them a glossy black appearance. They are useful in cases of anæmia accompanied with amenorrhœa; dose, from 1 to 5 pills two or three times a day.

Fructus Colocynthidis, colocynth. Poma Colocynthidis, of the size and shape of an apple, is the fruit of *Citrullus colocynthis*, a species of cucumber cultivated in Southern Europe, Africa, &c. Its poisonous qualities were known to the Jews, for when there was a dearth in the land the sons of the prophets could not eat thereof.[2] The chief constituent of colocynth is a bitter glucoside, colocynthin. The fruit or pulp is said to produce watery evacuations from the intestines, and to develop energetic peristaltic movements without causing any injurious effects, and espepecially without disturbing the stomach. It is used with temporary benefit in all forms of dropsy in which the effusion cannot be lessened either by general treatment or by acting on the heart or kidneys. It is said, however, to induce

[1] R. Kohn, 'Berl. klin. Wochenschr.,' 1882, S. 68.

[2] 2 Kings iv, 39.

congestion of the kidneys. Colocynth is given as a hot infusion of about 1 part in 150 of water, and generally in combination with diuretics. The maximum single dose is 0·3 gramme (4½ grains). The drug loses its efficacy by being kept any length of time. The preparations are—(1) TINCTURA COLOCYNTHIDIS. Dose, from 0·25 to 1 gramme (4 to 15 minims). (2) EXTRACTUM COLOCYNTHIDIS. Dose, from 0·01 to 0·05 gramme (⅙ to ¾ of a grain). Generally given in combination with other purgatives.

GUTTI, Cambogia, gamboge. The yellow gum-resin of *Garcinia morella*, a tree belonging to the Nat. Ord. Guttiferæ, growing in Siam. The resin, or gambogic acid, $C_{20}H_{24}O_4$, which constitutes about 70 per cent. of the drug, is one of its active ingredients. It appears itself to have no acrid or irritant properties, but to acquire them in the intestinal canal. According to Buchheim fat and bile, especially the latter, are necessary for their development.[1] The products resulting from its combination with these substances are as yet unknown; we only know that they set up violent irritation in the intestines. In ordinary doses gamboge does not appear to disturb the digestive function. In both respects its action is similar to that of colocynth. It is usually prescribed in doses of 0·05 to 0·3 gramme (¾ to 4½ grains) in pills. Gamboge is also included as a yellow pigment in paint-boxes, and if swallowed by children may set up inflammation of the intestines.

OLEUM CROTONIS, croton oil. Extracted from the seeds of *Tiglium officinale*, a small tree belonging to the Nat. Ord. Euphorbiaceæ, growing in the East Indies. It is a fatty oil of a brownish colour and acid reaction, containing several volatile and fatty acids with their glycerides, as well as tiglinic acid (methyl-crotonic acid, $C_5H_8O_2$) and crotonolic acid, $C_9H_{14}O_2$. The last appears to be the active principle.[2] The glycerine compound, which is inactive, is decomposed by the pancreatic ferment, and the liberated acid, even

[1] For a detailed account of most of these substances cf. R. Buchheim's treatise "Die Scharfen Stoffe," 'Arch. d. Heilkde.,' 1872, Bd. xiii, S. 1, and Bd. xiv, S. i.

[2] Flückinger, 'Pharmac. Chemie,' 1888, S. 211; cf. also Kobert's 'Arbeiten d. Pharmak. Instit. zu Dorpat,' 1890, iv, S. 5.

when combined with the alkali of the small intestine, acts as a powerful irritant. In many cases a quarter of a drop of croton oil is sufficient to produce watery evacuations. The maximum dose is 0·05 gramme ($\frac{3}{4}$ of a drop), and the best mode of administering it is either as a pill or mixed with some fatty oil. As it acts so violently, great caution is necessary in prescribing it. The dose, at first, should not be more than 0·005 to 0·01 gramme ($\frac{1}{12}$ to $\frac{1}{6}$ of a drop).

THE SECRETION OF BILE (as observed in healthy dogs) is increased in a greater or less degree by certain drugs. I have already referred to some which possess this property, and I will here once more briefly enumerate them:—Aloes, rhubarb, ipecacuanha, colocynth, jalap, podophyllin, benzoate of sodium, salicylate of sodium, tartarated soda, sulphate of sodium, phosphate of sodium, and perchloride of mercury—but, strange to say, not calomel, which merely stimulates the secretion from the intestinal glands. Purgatives, which increase the secretion from the intestinal glands—among which are sulphate of magnesium, gamboge, and castor oil,—diminish the secretion of bile. These are the conclusions arrived at by W. Rutherford, whom I have already quoted; but some of his results have since been called in question, and the list of substances, moreover, has been supplemented by others whose actions have been investigated.[1]

THE ANTHELMINTICS are remedies which promote the expulsion of parasites from the intestinal canal. They are usually given in combination with purgatives; for this reason, that the parasites not infrequently are merely narcotised but not expelled by the anthelmintics. The anthelmintic most frequently used is—

FLORES CINÆ, Semen Cinæ, santonica. The dried un-

[1] H. Paschkis, "Ueber Cholagoga," 'Wiener med. Jahrb.,' 1884, S. 159; Prevost et Pinet, 'Revue med. d. l. Suisse rom.,' 1888, No. 5; E. Stadelmann, in the Dissertations of O. Muller, E. Mandelstamm and A. Loewenton, Dorpat, 1890.

expanded flower-heads of *Artemisia maritima*, a plant belonging to the Nat. Ord. Compositæ, collected on the plains of Kirghiz, in Turkestan. They have a strong, peculiar scent, and a bitter, somewhat camphoraceous taste. The principal constituent is santonin, $C_{15}H_{18}O_3$, a colourless substance which crystallises in small flat plates, and, though neutral in its action on test-papers, is capable of combining with bases. Dry santonin is tasteless; it is soluble in 5000 parts of water, in 44 of alcohol, and in fatty oils. If exposed to the light it turns yellow. It was discovered by Kahler and Alms in 1830, and is a derivative of naphthalin.

Santonin is a specific remedy against the *Ascaris lumbricoides*. If a living round-worm is placed in a solution of santonin outside the body, no effect is produced upon the worm for a considerable time. It has therefore been assumed that santonin does not kill the parasite, but creates discomfort for it in the small intestine; it consequently descends into the large intestine, and then passes out along with the fæces, or, better still, is expelled by the aid of cathartic remedies.[1] Nevertheless the parasites are often either dead or in a narcotised condition when passed. The possibility, therefore, must not be excluded that in the intestines, santonin may be partially converted into a substance which has a directly poisonous action upon them, a change which would of course not necessarily take place in a simple solution outside the intestine.

Trochisci Santonini are officinal. These are lozenges made with sugar or chocolate, and containing 0·025 gramme ($\frac{3}{8}$ of a grain) of santonin.[2] The maximum dose of santonin is 0·1 gramme ($1\frac{1}{2}$ grains), and 0·5 gramme ($7\frac{1}{2}$ grains) the largest amount that may be given in one day. In former times santonate of soda, $NaC_{15}H_{19}O_4 + 7H_2O$, a colourless crystalline salt, was also officinal. As, however, this salt is very soluble in water, and consequently can hardly reach the lower part of the intestine, its use has been abandoned.

[1] W. v. Schroeder, 'Arch. f. exper. Path. u. Pharmak.,' 1885, Bd. xix, S. 290; Küchenmeister, 'Arch. f. physiol. Heilk.,' 1851, Bd. x, S. 630; F. Coppola, 'Cbl. f. klin. Med.,' 1888, S. 334.

[2] The Trochisci Santonini, Ph.B, each contain one grain of santonin.

FLORES CINÆ was formerly given in doses of a teaspoonful. The ethereal oil, however, which it contains has a nauseous taste and smell, and is superfluous as far as any effect on the ascarides is concerned. According to Rose, this oil acts upon rabbits as a deadly poison, 2 grammes causing paralysis of the nerve-centres, convulsions, and albuminuria.

If the dose of santonin be not too small, it imparts a greenish tint to the urine, and as the latter decomposes, the colour (owing to the formation of ammonium carbonate) changes to a rich red. The same change of colour is produced by adding any alkali to the urine.

I have already, in speaking of rhubarb and senna, referred to the discoloration of the urine which occurs after taking chrysophanic acid. Under ordinary circumstances, the tests I then described are sufficient for all practical purposes, as it is generally known what drug has been taken. For an account of more delicate tests and their application I refer you to the papers of Penzoldt and Jaffé.[1]

The administration of santonin, ESPECIALLY WHEN THE INTESTINE IS EMPTY, may produce acute poisoning, several instances of which have been recorded.[2] I was myself called upon to treat a case of this kind.

The patient, a very delicate child two years of age, was seized with violent convulsions ten hours after taking two chocolate pastilles, each said to contain 0·025 gramme ($\frac{3}{8}$ of a grain) of santonin. The attacks began with frequently recurring facial spasms, which then spread to the limbs, and finally, for some time, very distinctly interfered with the respiration. The irritation evidently originated in the region between the third and seventh pairs of nerves. The pupils were widely dilated ; the urine exhibited the usual greenish discoloration. I saw the case when the attacks were most marked. Warm baths and vinegar enemas were of no avail; artificial respiration, however, seemed to ward off impending death. The attacks recurred at intervals for three days,

[1] Penzoldt, 'Sitzungsber. d. Phys.-med. Soc. zu Erlangen,' vol. xxviii, Juli, 1884; M. Jaffé, 'Zeitschr. f. klin. Med.,' 1890, Bd. xvii.

[2] Cf. C. Binz, "Santoninvergiftung und deren Therapie," 'Arch. f. exper. Path. u. Pharm.,' 1877, Bd. vi, S. 300; Doctordiss. von P. Becker, 1876.

gradually decreasing in intensity and frequency, the urine remaining of a greenish colour all the time.

This case convinced me that we have no certain knowledge as to the proper method to be adopted in treating cases of poisoning of this character, and so induced me to make some exhaustive experiments on animals. The result showed that warm-blooded animals in general are affected by santonin precisely in the same way as human beings; and further, that by the administration of ether, chloroform, and chloral hydrate the convulsions could be limited in duration, or even cut short at the outset.

Here is a rabbit weighing about 600 grammes, to which half an hour ago I gave a subcutaneous injection of 0·6 gramme of sodium santonate. Every two or three minutes it has violent convulsions, but each attack is prevented or mitigated, as I have stated, by the administration of ether. For obvious reasons, the same treatment is likely to be suitable for human beings. In any case of the kind, therefore, artificial respiration should be kept up till ether or chloroform can be procured, and after the immediate danger has been averted, chloral may be given in carefully adjusted doses. To eliminate the poison give cathartics, and let the patient have large quantities of liquid to drink.

If a full dose of sodium santonate is injected into the veins of a warm-blooded animal, the circulation through the brain and medulla oblongata having been stopped by ligaturing the carotids whilst life is maintained by artificial respiration, convulsions will be produced in the parts supplied by the nerves issuing from the spinal cord. After such doses the heart still continues to act regularly; the convulsions cannot, therefore, arise from asphyxia. Consequently, under certain circumstances, santonin is a poison which causes spasms by its stimulating action on the spinal cord (B. Luchsinger). This my own experiments [1] had already demonstrated.

The second pair of cranial nerves are also affected by santonin, even in non-poisonous doses. All white or brightly illumined objects appear yellow or greenish yellow. This is

[1] C. Binz, 'Arch. f. exper. Pathol. u. Pharmak.,' 1889, Bd. xxv, S. 367.

the change most commonly observed: in some cases red and blue are replaced by their complementary colours, green and orange; crimson becomes fawn; scarlet, the colour of bronze; blue acquires a greenish, and green a violet tinge. E. Rose[1] distinguishes between two forms of disturbed vision; yellow vision, in which yellow predominates in all compound colours containing yellow and violet; and violet vision, a sign of more intense poisoning, in which all objects appear to vary from violet to ultramarine, according to their depth of tone.

By way of explanation, this phenomenon has been associated with a fact to which I have already referred, namely, the change to a yellow colour which santonin undergoes on exposure to the light. It was suggested that the yellow santonin simply permeated those parts of the eye which absorb and refract the light, and so acted like a yellow glass. Among other objections to which this theory is open, is the fact that both picric acid and jaundice impart a yellow colour to the serum in the tissues without causing yellow vision. The altered vision is simply due to functional disturbance of the optic nerve, or of its central or terminal endings, and is often accompanied with dizziness and unconsciousness. It was noted in a cachectic individual twenty years of age that aphasia accompanied the yellow vision. In another case of CHRONIC santonin poisoning—the patient being a boy of eleven—the power of speech was entirely lost. He also suffered from paralysis of the large muscles, alternating with spasms. The symptoms continued for some weeks after the santonin had been discontinued.[2]

Next in order are the officinal remedies used for expelling the tapeworm,—male fern, pomegranate bark, kousso, and kamala.

RHIZOMA FILICIS, fern root. The rhizome of *Aspidium filix-mas*, gathered in autumn with the bases of the foot stalks, and cleared of the root fibres and scales. It has a sweetish, astringent, and rather bitter taste, and very little

[1] E. Rose, 'Arch. f. pathol. Anat.,' 1859—1864, Bd. xvi, S. 233; Bd. xviii, S. 15; Bd. xix, S. 522; Bd. xx, S. 245; Bd. xxviii, S. 30; Bd. xxx, S. 442.

[2] Van Rey, 'Therap. Monatshefte,' 1889, S. 532.

odour. It was known to the ancients and used by them, and still maintains its position as a remedy.

In the year 1775 Louis XVI paid 18,000 francs to the widow of the Swiss surgeon Nuffer, for a secret remedy for tapeworm, the principal ingredient of the remedy being *Filix mas*; and Frederick the Great purchased a similar remedy from Matthieu, a Swiss apothecary, with an annuity of 200 thalers (£30) and the title of Aulic Councillor. The active principle in the plant is supposed to be FILICIC acid, $C_{14}H_{18}O_5$, which is obtained in a crystalline form from the granular masses which separate from the officinal ethereal extract of the root after it has been kept for some time. This view, however, is denied,[1] on the ground that extracts of the root which only contained traces of filicic acid were found to be very efficacious. The drug contains another ethereal oil, together with some resin and tannic acid. It is maintained that the resin and oil[2] also possess anthelmintic properties, and that therefore the rhizome itself is the best form in which to administer the drug.

Besides the rhizome the EXTRACTUM FILICIS is officinal. The latter is a greenish liquid, extracted by means of ether, and insoluble in water. The root is given as a powder, &c., in doses of 5 grammes (75 grains), repeated several times at short intervals; a single dose only of the extract of 1 to 3 grammes (15 to 45 minims) is given, which is generally mixed with the powdered root and made up into pills.

The ethereal extract has also proved a reliable remedy for the intestinal parasite, *Dochmius* or *Anchylostoma duodenale*, which produces the anæmia, common in Northern Italy, among miners and labourers in tunnels or brick-kilns. If the larvæ are immersed in the extract they die within five or ten minutes.[3] The statement that it acts beneficially when given to human beings has been confirmed by various authorities.[4]

[1] L. Reuter, 'Pharm. Ztg.,' 1891, Bd. xxxvi, S. 245; 'Ref. Chem. Ztg.,' 1891, 2 Mai.

[2] Frohner, 'Monatsh. f. pr. Thierheilk.,' 1891, Bd. i, S. 1.

[3] E. Perroncito, 'L' anemia dei contadini, fornaciai e minatori in rapporto coll' attuale epidemia negli operai del Gottardo,' Turin, 1881, p. 154.

[4] For reports on the subject see H. Menche, 'Zeitschr. f. klin. Med.,'

In the treatment of persons troubled with this parasite, or with tapeworm, it cannot be too strongly insisted upon that, if the first dose of the powder or extract fail to expel the parasite, and a second dose of the remedy is administered, special care should be taken that the drug, whether in the form of powder or extract, should be quite fresh, as by keeping, the activity of the remedy is entirely destroyed.[1]

Large doses of the extract, such as from 10 to 20 grammes (2½ to 5 drachms), which are often necessary in the treatment of tapeworm, and usually in that of Dochmius, are not always free from risk. Menche, six hours after the administration of a dose of 20 grammes (5 drachms), detected a considerable amount of albumen, as well as cylindrical casts, in the urine, the secretion of which was considerably diminished; twelve hours later, however, the kidneys were again acting normally. Another observer[2] witnessed the development of violent intestinal irritation, a febrile temperature with a pulse-rate of 144 to the minute, marked coma, threatened collapse, and temporary blindness after the return of consciousness, following upon the administration of 7·5 grammes (about 2 drachms) of the freshly prepared extract and 7·5 grammes of the powder to a female twenty-two years of age. These symptoms continued for about five days; their severity was said to be owing to the patient's bowels being constipated at the time, so that the remedy was retained there too long; the suggestion has therefore been made, that the administration of the male fern should always be supplemented by a full dose of castor oil; but this practice is attended with some risk, as filicic acid is soluble in the fatty oils, and in a soluble form would be all the more rapidly absorbed. In the same way, large doses of the liquid extract are especially dangerous if there is any gastric or intestinal lesion through

1883, Bd. vi, S. 161; and G. Mayer, 'Cbl. f. klin. Med.,' 1885, S. 265.

[1] O. Leichtenstern, 'Deutsche med. Wochenschr.,' 1885, S. 525.

[2] Schlier, 'Münch. med. Wochenschr.,' 1890, S. 553. A delicate girl of five and a half years old died from stupor and convulsions, about six hours after taking 7·5 grammes (about 2 drachms) of the extract; v. Hofman, 'Ref. Cbl. f. klin. Med.,' 1890, S. 933; E. Poulsson, 'Arch. f. exper. Path. u. Pharmak.,' 1891, Bd. xxix, S. 11; E. Grawitz, 'Berl. klin. Wochenschr.,' 1894, No. 52.

which the remedy may be more rapidly absorbed, a danger which has in several instances been recently demonstrated. It has, moreover, been asserted that the remedy has a destructive action on the red blood-corpuscles, and may occasion severe jaundice.

Cortex Granati, pomegranate bark, is obtained from the *Punica granatum*, a bush or tree belonging to the Nat. Ord. Myrtaceæ, a native originally of Western Asia, but now also cultivated in Europe as an ornamental plant. The bark of the stem, as well as that of the root, is now used, though formerly that of the root alone was officinal. This part of the plant was used, even in ancient times, to expel tapeworm from the intestines; it then gradually fell into disuse, until attention was again directed to it in the first half of the present century, and in 1846 the root-bark was included in the Prussian Pharmacopœia.

The chief constituent of the bark is an alkaloid, which was separated in 1844 by Righini in an impure state. He described its characters, and named it Punicin; in 1878 it was prepared, in a pure state, by Tanret of Troyes, and by him named Pelletierin.[1] I prefer the former name, as it is shorter, and also because the latter may give rise to mistakes.[2] The chemical formula of punicin is $C_8H_{15}NO$; it is a volatile base, and forms salts which readily crystallise. Besides punicin, the bark contains isopunicin, $C_8H_{15}NO$ (isopelletierin), and two other bases which have no therapeutic value, and are therefore, as far as we are concerned, of little importance. They merely possess the poisonous properties of the first two, and those only in an attenuated degree. Tanret named them Pseudo-pelletierin, $C_9H_{15}NO$, and Methyl-pelletierin, $C_9H_{17}NO$. Tannic acids are also contained in pomegranate bark, and are of practical importance, as the salts they form with punicin are not readily soluble.

If a *Tænia serrata*, the tapeworm of cats, is put, when fresh from the intestine, into water at 37° C. (98·6° F.) containing 1 per cent. of sodium chloride and 0·1 per cent. of sodium carbonate—a solution which is not injurious to it,—and 0·01 per cent. of punicin is then added to the liquid,

[1] Tanret, 'Comp. rend.,' vol. lxxxvi, p. 1279; and vol. lxxxvii, p. 358.

[2] F. A. Falck, 'Arch. d. Pharmacie,' 1879, Bd. xi, Heft 6.

the animal within five minutes loses the power of movement. If it is now placed in a fresh warm solution of the sodium salts, without punicin, it will recover its motor power in about thirty minutes. If left longer than ten minutes in the solution of punicin, it remains motionless and dies.[1] These effects correspond with those produced on the parasites, after the administration of the remedy to patients in the Paris hospitals. Out of eighty-eight cases, eighty-two were treated successfully; that is to say, the head of the tapeworm was expelled. It is to be remarked, however, that this took place only in those cases in which, together with the punicin (0·4 to 0·5 gramme [6 to 7½ grains] of the sulphate), 0·5 gramme (7½ grains) of tannic acid had been given. When the head was not expelled, the punicin sulphate, being readily soluble, was (as we are justified in assuming) absorbed in the upper part of the intestine, and so did not come in contact with the tænia.

It has often been observed that nausea, vomiting, and unconsciousness have resulted from the administration of large doses of pomegranate bark. This is due to the alkaloids which it contains. If a dose of 0·5 gramme (7½ grains) of punicin be given to an individual uncombined with tannic acid, it will produce the following effects:—dizziness, dimness of vision, and a sense of weakness in the limbs; sometimes also, but not invariably, it will produce nausea, vomiting, twitchings, and contractions of the muscles in certain regions, and especially of the gastrocnemii.[2]

Hitherto pomegranate bark has been given as a decoction of 25 to 40 parts in 200 grammes (from 6 to 10 drachms in 8 ounces) of water. A better plan is to give a mixture of punicin and tannic acid, but the high price of the punicin is an obstacle to its general use.[3]

Flores Koso, kousso flowers. These are the dried panicles (chiefly of the female flowers) of *Hagenia abyssinica*, a tree belonging to the Nat. Ord. Rosaceæ, and growing in

[1] W. v. Schröder, 'Arch. f. exper. Path. u. Pharmak.,' 1884, Bd. xviii, S. 381.

[2] Cf. v. Schröder's paper, just referred to, in which the experiments of Dujardin-Beaumetz and others are discussed.

[3] Senator, 'Berl. klin. Wochenschr.,' 1884, No. 1.

Abyssinia. The flowers have a faint aromatic odour, and an acrid, bitter taste. Their efficacy is said to be due to a yellow crystalline substance named kosin, the composition of which is $C_{31}H_{38}O_{10}$. It is a feeble acid, insoluble in water, and only slightly soluble in alcohol. This preparation, however, has not been received with much favour. The dose, to be effectual, should consist of the unstrained infusion of 15 to 20 grammes (3½ to 5 drachms) of the flowers in 7 to 10 ounces of water, and such a dose is not readily swallowed. Rosenthal (Erlangen) recommends the use of compressed tablets of the flowers. Each one weighs 1 gramme (15 grains), and is small enough to be swallowed without difficulty. I have used these tablets, giving twenty for a dose, with good results in two cases; warm water was administered simultaneously, and an aperient subsequently. Nausea, abdominal pain, vomiting, and diarrhœa are caused by too large a dose.

The kousso tree is cultivated with much care by the Abyssinians, as, in consequence of their free indulgence in raw meat, and in another filthy habit,[1] the tapeworm—*Tænia saginata*—which is more resistent to remedies than other forms, is quite common among them, and is even regarded as a beneficent *spiritus familiaris*.

KAMALA is the minute glands and hairs obtained from the surface of the fruit of *Malleolus phillipinensis* (*Rottlera tinctoria*), a shrub or tree belonging to the Nat. Ord. Euphorbiaceæ, growing in the East Indies. It is a light, mobile powder of a red colour mixed with grey, and without either taste or smell. If slightly magnified, it is seen to consist of irregular spherical glands arranged in rays, and enclosing forty to sixty club-shaped cells. With the glands are mixed thick-walled, colourless, stellate hairs, but fragments of leaves and stalks should not be present.

From the earliest times kamala has been used in India as a dye for silk, but whether it was known to act as a poison on tapeworms is uncertain. About the middle of the present

[1] Cf. Schimper, in Leuckhart's 'Die menschlichen Parasiten,' 1876, Bd. ii, S. 855. For practical information about remedies for tapeworm cf. K. Bettelheim, in v. Volkmann's 'Sammlung klin. Vorträge,' 1879, Serie 8, No. 166.

century it was introduced as a remedy by English physicians. The active principle has not yet been isolated, although a substance named Rottlerin (Kamalin), $C_{20}H_{22}O_6$, a Rottlear red, and a resin have been obtained from it. The great advantage this remedy possesses is that it is entirely free from taste. I have found it of service in one case, as a cure for the *Tænia saginata* (*medio-cannelata*), which is not readily expelled. It is possible that in other cases where the remedy has not acted satisfactorily, the preparation was either adulterated or not fresh, or, if good, was given in too small a dose. The proper quantity is from 8 to 12 grammes (2 to 3 drachms) divided into two doses, and given with an interval of half an hour between them. It does not give rise to nausea, but causes the fæces to be somewhat loose and of a red colour.

SEMEN ARECA, areca or betel nut, is officinal as an anthelmintic in veterinary practice. It consists of the spherical or conical seeds of *Areca catechu*, one of the palms. The principal ingredient of it is arecolin, a poisonous alkaloid; another of its constituents, arecain, is not poisonous.[1]

DIURETICS, OR REMEDIES WHICH INCREASE THE FLOW OF URINE, have long been known and employed, but it is only within the last two or three decades that they have been systematically investigated and that their value has been determined. I have already, in discussing some of the remedies belonging to this class, referred to their mode of action. The importance of the subject, however, justifies me in briefly recapitulating the more salient features.

FOLIA DIGITALIS have a diuretic action, if the diminished urinary secretion is due to heart disease. Owing to the passive congestion of the kidneys as well as of other organs, which is associated with cardiac disease, there is a diminution of the quantity of urine secreted, and an increase in the quan-

[1] Marmé, 'Nachr. d. Ges. d. Wiss. Göttingen,' 1889, No. 7.

tity of lymph exuded into the cellular tissue. Digitalis, by equalising the circulation, removes the cause of both these conditions, and obviates the results which would follow from them. It has no direct effect upon the kidneys nor upon the process of secretion, neither does it, in healthy animals, act indirectly by increasing the blood-pressure. It acts, therefore, as a diuretic only in cases of heart disease. This statement applies equally to squills and strophanthus.

DILUTE ALCOHOL has a strong diuretic action. After the administration of 1 litre of water to a healthy young man, the urine passed within five hours amounted to 385 c.c.; after 1 litre of water charged with carbonic acid it amounted to 629 c.c.; after 1 litre of Munich beer to 1012 c.c.; and after 1 litre of wine to 1600 c.c. The administration of a decoction of hops induced an irritable condition of the bladder, but no marked diuresis. The diuretic action of alcohol, which, as we know, is very distinct, shows itself in full force only when the blood is well charged with water by the simultaneous administration of large quantities of this liquid, for 0·1 of a litre of a 40 per cent. solution of alcohol produced in the time above mentioned only 553 c.c. of urine, while 1 litre of a 4 per cent. solution produced 961 c.c.

How this effect is produced we do not know, but in any case there is local irritation, for habitual and excessive indulgence in alcohol gives rise to nephritis.

CAFFEINE and the salts of theobromine are powerful diuretics; they act by stimulating the secretory activity of the epithelium in the renal tubules.

That the effect is produced in this way is proved by the fact that the same result follows the administration of these remedies, when the renal vessels are paralysed either by a previous dose of choral hydrate, or by section of the nerves distributed to the kidneys. Nothing then is left but the epithelium for the caffeine to act upon.

CALOMEL is also at the present time frequently employed as a diuretic. The fact that it does act in this way is undoubted; why it does so is by no means clear. Possibly the mercurial compound causes the renal vessels to dilate, an effect which has been noted in experiments made with compounds of silver and platinum. Whereas,

for instance, the secretion of urine, after being increased by the administration of chloral hydrate, or by section of the renal nerves, is still further augmented by the administration of caffeine, no such effect is produced by these metallic compounds if the renal vessels have been previously paralysed. It is consequently probable that the diuretic effect of calomel is due solely to local dilatation of the renal vessels, and not to special stimulation of the renal epithelium such as is caused by caffeine and theobromine.

THE ETHEREAL OR ESSENTIAL OILS have been credited with diuretic properties from an early date, but not until recent times has the diuretic action of any of them been thoroughly investigated on healthy individuals.[1] The results obtained show that the oil of the berries of *Juniperus communis*, and that of the root of *Levisticum officinale* (heartwort) are efficacious in doses of 0·2 to 0·4 gramme (3 to 6 minims), while similar doses of the oils obtained from the seeds of *Petroselinum sativum* (common parsley) and the root of *Archangelica officinalis* (garden angelica) are still more effective. Contrary to expectations, no diuretic effects followed a dose of 0·4 gramme (6 minims) of oil of turpentine, though the action was distinctly marked after 1 gramme of turpin hydrate.

The composition and dose of SPECIES DIURETICÆ, diuretic tea, a compound of diuretic remedies, have been referred to in vol. i, p. 378.

SPIRITUS ÆTHERIS NITROSI, which is substantially pure ethyl nitrite combined with a large proportion of alcohol (see vol. i, p. 19), has long been used as a diuretic. Its action has, however, not yet been fully investigated.

The secretion of urine is also augmented by some of the alkaline salts of the Pharmacopœia; by those, for instance, which are readily absorbed from the intestines, among which may be included chloride of sodium, acetate of potassium, tartarated soda, and nitrate of sodium. In some experiments on the effect of sodium chloride on the urinary secretion the following results were obtained: the average secretion of urine in a given period, when neither water nor

[1] Alex. Raphael, in Kobert's 'Arbeiten d. Pharmakol. Institut zu Dorpat,' 1894, x, 81—153.

chloride of sodium was taken, was 828 c.c.; but after taking 20 grammes of chloride of sodium, also without water, the secretion amounted to 1124 c.c. during the same period. The amount of urea was also somewhat increased.

References to the diuretic effects of the other alkaline salts will be found under their respective headings. Tartarated soda acts only slightly as a diuretic. Tartarated borax is much more active. Sugar of milk may also be included in this class of remedies.

XXIX.

Fatty oils—Emulsions—Fats—Glycerine—Wax—Vaseline—Gum arabic and its congeners—Cod-liver oil.

EMOLLIENTIA is the name given to remedies which relax the surface of the skin and mucous membranes, or which serve to protect parts deprived of their epidermis or epithelium, from the action of the air, the secretions, or foreign bodies with which they may be brought in contact. We may include among the emollient remedies the fatty oils and fats, gums, starch, &c., and preparations containing them. I have already (see vol. ii, pp. 24, 25) discussed the composition of the fatty oils and fats, so far as we are concerned pharmacologically with them.

In the older pharmacopœias the number of remedies included in this class was very large. Those still retained in the German Pharmacopœia are—

AMYGDALÆ DULCES, sweet almonds, the seeds of *Prunus amygdalus*, a tree belonging to the Nat. Ord. Amygdaleæ and growing on the shores of the Mediterranean. The principal ingredients of sweet almonds are a fixed oil, consisting almost entirely of olein, a compound of oleic acid—$C_{18}H_{34}O_2$,—an albuminous substance (emulsin), and sugar. Almonds are given in the form of emulsion; 20 to 30 grammes (6 to 8 drachms) of them are peeled, rubbed lightly in a mortar to a smooth consistence, and then mixed with ten times their weight of water. To give the preparation a pleasant taste, after straining it, the officinal SIRUPUS AMYGDALARUM or Sirupus emulsivus—made of sweet almonds and sugar, and flavoured with a small quantity of bitter almonds—is often added. Mixed with water this emulsion forms milk of almonds, and is taken as a beverage. The emulsion can also be prepared from the officinal OLEUM

AMYGDALARUM. The oil forms about half the weight of the almonds. It is a thin, pale yellow liquid, lighter than water, freezes only at a very low temperature, and when fresh has a bland nutty taste.

An EMULSION is a liquid in which an insoluble substance of an oleaginous nature is held in suspension. In the present instance this results from the subdivision of the lighter substance, the oil, into very minute particles, and from each being enclosed in a layer of vegetable casein or gum which prevents them from uniting. The drops thus remain small, and therefore rise very slowly to the surface; for the smaller the fatty particles are, the greater is their superficies in proportion to their mass—according to the mathematical ratio of spherical bodies,—and the greater, consequently, the resistance they have to overcome in rising in a liquid of greater specific gravity. When the emulsion is made with the seed it is prepared, unless otherwise ordered, with 1 part of seed and enough water to produce 10 parts of the strained liquid; when the emulsion is made with the oil it consists of 2 parts of oil, 1 of powdered gum arabic, and 17 of water.

Oil of sweet almonds is given alone, in doses of one or two teaspoonfuls, as a mild aperient for children. Its effect is most likely due to some of the products resulting from its decomposition in the intestine. It has also been proposed to inject it subcutaneously, as nourishment, in cases of obstruction of the primæ viæ. Whether it would be absorbed quickly enough to be of service, is doubtful.

OLEUM OLIVARUM, olive or Provence oil. This is the oil, expressed without heat, from the fruit of the *Olea europæa*. It has a faint odour, a pleasant taste, and a colour tinged with green from the chlorophyll in the pulpy part of the fruit. At a temperature of about 10° C. (50° F.) olive oil begins to grow turbid from the formation of crystals, and at 0° C. (32° F.) it becomes thick, and has the consistency of ointment. About two thirds of the oil consists of olein; the remainder is chiefly palmitin, with a slight admixture of stearin and butin. Only the best olive oil, absolutely free from any suspicion of rancid taste or smell, can be administered internally; when rancid it causes diarrhœa, even if made up into an emulsion with gum arabic. For external

use and for veterinary purposes Oleum Olivarum Commune, common olive oil, may be employed. Less care is exercised in preparing and storing it.

From experiments on dogs, and from clinical observations on patients suffering from gall-stones, the conclusion has been drawn [1] that the effect of large doses of oil is greatly to increase the secretion of bile, and considerably to diminish its consistency, far exceeding in these respects the results produced by any other cholagogue. The amount of the best salad oil given to a patient was from 100 to 180 grammes (about 3 to 5½ ounces) a day. After the oil has been taken, peculiar lumps mixed with bile are found in the evacuations, some of them pultaceous, and some of them soft but shaped—the so-called pseudo-calculi. They consist of saponified fat, and are formed, according to Virchow, by the oil passing from the intestine into the liver, and being taken up and transmuted by the epithelium of the biliary passages.[2]

In many cases the administration of large quantities of oil induces acute dyspepsia, notwithstanding the brandy and menthol which are usually given with it.

This method of treating individuals suffering from gall-stones is said to have originated in 1882 with Kennedy, in Canada.

Semen Lini, linseed, the seed of *Linum usitatissimum*, belonging to the Nat. Ord. Linaceæ. Glossy oval seeds of a brown or yellowish colour, from 4 to 6 mm. in length, with a bland, oily, but not rancid taste. The principal ingredient is Oleum Lini, linseed oil, which is of a yellow colour, and dries quickly when exposed to the air. It consists mainly of glycerine and fatty acids, more especially linoleic acid. The seeds contain about 30 per cent. of oil. When ground down and deprived of the greater part of the oil they form linseed meal, which is used externally, chiefly in the form of poultices, to promote suppuration.

[1] B. Rosenberg, 'Therap. Monatshefte,' 1889, S. 542; 'Berl. klin. Wochenschrift,' 1889, Nos. 48 and 49; 'Arch. f. d. g. Physiol.,' 1889, Bd. xlvi, S. 334.

[2] Fürbinger, 'Verhandl. d. Congr. f. innere Med.,' Wiesbaden, 1891, S. 63.

For this purpose the chief requisite is warmth. The poultices can generally be borne at a temperature as high as 50° C. (122° F.). Their effect is to stimulate the activity of the white blood-corpuscles, and to cause them to emigrate more rapidly and in greater numbers. An abscess is thus formed more quickly, the pus comes to the surface and is discharged, and the inflammation subsides. To prevent the poultice from cooling too rapidly, the amount of moist linseed enclosed in a linen bag or wrapper should not be too small. The poultice should not be less than 2 cm. (¾ of an inch) thick. Over this may be placed with advantage some material which is a bad conductor of heat, such as a piece of oiled silk, and this should be covered with flannel.

Linseed meal formerly bore the officinal name of Farina Seminis Lini. At present the PLACENTA SEMINIS LINI, or linseed-meal cake, is prescribed in Germany; it is the hard grey residue left after the seeds have been pressed.

SEMEN PAPAVERIS, poppy seed, obtained from *Papaver somniferum* (Papaveraceæ). Whitish reniform seeds, 1 mm. long, the constituents of which are much the same as those of the sweet almond. The poppy seeds can be employed for the same purposes, and may be given in the same dose and in the same fashion as sweet almonds; the only difference between them being that the former contain 0·06 per cent. of morphine.

OLEUM PAPAVERIS, poppy oil, has a pale yellow colour, and a mild taste, and soon dries on exposure to the air. It consists mainly of glycerine and an acid closely allied to linoleic acid.

The seeds of one species of Papilionaceæ which belongs pharmacologically to this group are officinal — SEMEN FŒNUGRÆCI, the seeds of *Trigonella fœnum-græcum*, fenugreek, which comes originally from the East, but is cultivated in Europe. They contain mucilage, fatty oil, and some aromatic resin, and are used in veterinary practice.

Of solid fats the following are officinal:

ADEPS SUILLUS, hog's lard, the internal fat of the abdomen of the hog, separated by melting from the membranous matter, washed, and dried. It has a soft and uniform consistence, melts at 36° to 42° C. (96·8° to 107·6° F.) to a clear,

colourless liquid which has no rancid odour. About 60 per cent. of it is olein, the remainder palmitin and stearin.

SEBUM OVILE, mutton suet, a white solid fat, melting to a clear liquid at about 47° C. (116·6° F.). It has a peculiar but not rancid smell, and consists for the most part of stearin, with but little of the other two glycerides.

OLEUM CACAO, Oleum Theobromatis, cacao butter, is the concrete oil of the seeds of *Theobroma cacao*. It melts at 31° to 32° C. (87·8° to 89·6° F.), and is harder than mutton suet. It consists chiefly of stearin, with an admixture of some other glycerides.

CETACEUM, spermacèti, the concrete fatty substance contained in the cranial cavities of cachalots, especially *Physeter macrocephalus*, purified by pressure and crystallisation. It consists of broad, crystalline, foliaceous plates, composed mainly of cetyl palmitate (cetyl alcohol = $C_{16}H_{33}.OH$), which melt at 45° to 50° C. (113° to 122° F.), and form a clear, colourless liquid with a faint odour.

OLEUM NUCISTÆ, or Oleum Myristicæ, nutmeg butter, or oil of mace, is the oil expressed from the seed-kernels of *Myristica fragrans*, and consists mainly of the glyceride of myristic acid, $C_{14}H_{28}O_2$. It also contains an ethereal oil and colouring matter, is of a reddish-brown colour, and melts at 45° to 51° C. (113° to 123·8° F.). It is the basis of Balsamum Nucistæ, nutmeg balsam. This is prepared by melting together oil of mace, olive oil, and wax in a vapour-bath; the compound is then filtered and poured into capsules. It is brownish yellow, and has an aromatic odour.

Mixed with lard, suet, wax, oil of rosemary, and oil of juniper, oil of mace forms a yellow ointment, UNGUENTUM ROSMÀRINI COMPOSITUM.

The ethereal oil of rosemary is obtained from the leaves of *Rosmarinus officinalis*, a shrub (Labiatæ) growing in southern climates.

There still remains to be mentioned the OLEUM LAURI, which is used in Germany as an aromatic liniment. It is obtained by pressure from the fruit of *Laurus nobilis*, the bay tree, and is a green, unctuous mixture of fat and ethereal oil. The fat is for the most part the glyceride of lauric acid, $C_{12}H_{24}O_2$.

A substance of special importance which is obtained from fat is—

GLYCERINUM, glycerine, $C_3H_5(OH)_3$; a clear, colourless, odourless liquid, of syrupy consistence, sweet to the taste, and of neutral reaction; soluble in all proportions in water and alcohol, but insoluble in ether, chloroform, and fatty or ethereal oils. It is a triatomic alcohol. In a pure state it is hydroscopic and viscid. The specific gravity of the officinal preparation is about 1·230, which corresponds to the presence of about 13 per cent. of water; the specific gravity of anhydrous glycerine is 1·265.

Fats, if exposed to the action of super-heated steam, are decomposed, with the absorption of water, into glycerine and the corresponding acids. The same change takes place when they are boiled with water and alkaline bases, except that the liberated acids then combine with the bases to form compounds which, according to the solubility or insolubility of the base, are termed SOAPS or PLASTERS (Scheele discovered glycerine in 1779 in preparing ordinary lead plaster.) By treating fat with sulphuric acid, glycerine is also separated, sulphoglyceric acid being formed, which is decomposed by the addition of lime. Many substances, insoluble in water, are partially soluble in glycerine, such as sulphur, iodine, and phosphorus. It is often advantageously used as a basis for ointments, as it neither dries up nor becomes rancid. It causes pain, however, if applied to ulcerated surfaces. The application of anhydrous glycerine, for example, to the inner surface of the uterus has been followed by severe irritation, absorption of glycerine by the blood, destruction of the red corpuscles, and nephritis.

Glycerine is one of the constituents of fermented liquors, being present, for instance, in pure wine in proportions varying from 0·7 to 1·6 per cent.[1] It is formed when fatty foods are heated, and when they are decomposed in the intestine by the action of the pancreatic ferment. It has therefore been regarded as a food similar to cod-liver oil. The results of experiments[2] made on this point prove that if given in moderate

[1] Neubauer und Bergmann, 'Zeitschr. f. analyt. Chemie,' 1878, Bd. xvii, S. 442.

[2] J. Munk, 'Arch. f. pathol. Anat.,' 1879, Bd. lxxvi, S. 119; L.

quantities it is completely oxidised in the system, but that it appears in the urine if large doses are administered. Unlike fat and carbo-hydrates, it does not diminish the albuminous waste. The urine is increased in amount, and contains some substance which reduces cupric oxide, but which is not glucose. If injected subcutaneously into the bodies of animals, glycerine readily causes hæmoglobinuria, by dissolving the red blood-corpuscles.[1]

The following case[2] is instructive as showing how far glycerine can be tolerated by human beings.

A teaspoonful of glycerine was given every hour to a man who had eaten a sausage containing trichinæ, and in whose fæces trichinæ were discovered. A cathartic had been previously administered, and the patient was kept on a restricted diet. He thus took nearly fifteen tablespoonfuls consecutively, that is upwards of 200 grammes in one day, "without any discomfort beyond a feeling of thirst, and dryness in the mouth and throat, which were alleviated by sipping seltzer water. Hæmoglobinuria did not occur; the remedy merely produced some thin, watery evacuations." The patient travelled home next day, provided with another 150 grammes of glycerine. He quickly recovered and remained perfectly well, while the other persons who had eaten the diseased pork suffered severely.

It is to be noted that adult *Trichinæ spirales* of ten days old, when placed in a mixture of glycerine and water (1 : 4), died within a quarter of an hour, and at the end of that time were noticeably shrivelled.[3] Of all remedies that have been tried on human beings suffering from trichinosis, glycerine has proved the least harmful.

Glycerine is well adapted to promote the evacuation from the colon and rectum of hard fæcal masses when these are

Lewin, 'Zeitschr. f. Biologie,' 1879, Bd. xv, S. 243; Tschirwinski, ibid., S. 252.

[1] Luchsinger, 'Arch. f. d. ges. Physiol.,' 1875, Bd. xi, S. 502; Ustimowitsch, ibid., 1878, Bd. xiii, S. 453; P. Plósz, ibid., 1878, Bd. xvi, S. 153; Schwahn, 'Eckhardt's Beiträge,' 1879, Bd. viii, S. 167; Filehne, 'Arch. f. pathol. Anat.,' 1889, Bd. cxvi, S. 413.

[2] G. Merkel, 'Arch. f. klin. Med.,' 1885, Bd. xxxvi, S. 357.

[3] A. Heller, v. Ziemssen's 'Handbuch d. spec. Pathol. u. Ther.,' 1874, Bd. iii, S. 376.

impacted there, and the contractile force is not energetic enough to expel them.[1] From 3 to 5 grammes (45 to 75 minims) are injected a few centimetres up the rectum, and this is very soon followed by increased peristaltic movement. The process is absolutely painless if the mucous membrane is in a healthy state. The action evidently is due to irritation of the rectum produced by the glycerine, the effect extending also to the large intestine.

The injection of glycerine into vascular tissue causes a marked contraction of the tissue.

Glycerine is frequently sold in an impure state, being adulterated generally with sulphuric acid, chalk, acrolein, and butyric acid, though these are usually present only in small quantities. Recently, however, considerable quantities of arsenic have been detected in it, due to impure sulphuric acid being used in its preparation. The German Pharmacopœia gives full directions for detecting the presence of these various adulterations.

Unguentum Glycerini, glycerine ointment. Prepared from glycerine, wheat starch, tragacanth, water, and alcohol. A transparent jelly, uniformly soft, and entirely free from odour.

Other ointments included in the Pharmacopœia are—

Unguentum Basilicum, basilicon ointment. Mainly composed of turpentine, with the addition of olive oil, wax, resin, and suet. Unguentum Cereum, simple ointment. A mixture of olive oil and yellow wax. Unguentum Leniens, cold cream; made with wax, spermaceti, oil of sweet almonds, water, and otto of roses.

Oleum Rosæ, otto of roses, which is used to perfume ointments, is a pale yellowish liquid in which, when cooled, transparent scale-like crystals are formed. These again liquefy when the temperature is raised to about 12° C. It is a compound of two oils,—one of them, which has not yet been closely examined, being a liquid ethereal oil containing oxygen; the other is concrete at ordinary temperatures. Four drops of otto of roses added to one litre of water forms the officinal Aqua Rosæ.

[1] Anacker, 'Deutsche med. Wochenschr.,' 1887, No. 37; C. Lüderitz, 'Berl. klin. Wochenschr.,' 1889, S. 283 (Versuche an Tieren).

A substance which is chemically related to the fats, and is often combined with them in ointments, is wax, Cera Flava and Cera Alba. It is made in the bodies of working bees from the food they take, and consists chiefly of myricyl palmitate ($C_{30}H_{61}.C_{16}H_{31}O_2$) and free cerotic acid ($C_{27}H_{54}O_2$), the former insoluble in alcohol, the latter soluble. At a temperature of 63° to 64° C. (145·4° to 147·2° F.) yellow wax melts to a clear, sweet scented, reddish-yellow liquid, which, upon solidification, presents under the microscope a confused crystalline appearance. When bleached it becomes white wax, but in other respects retains its properties. Wax is a substance that is little liable to change.

Essentially belonging to the same class are—

Unguentum Paraffini, paraffin ointment or vaseline. It is prepared by mixing one part of solid with four parts of liquid paraffin. It is white and transparent, of the consistence of ointment, and under the microscope is seen to be permeated with little crystals. It liquefies at a temperature between 40° and 50° C. (104° and 122° F.). It is well adapted for protecting wounds and as a basis for ointments, as it possesses absolutely no irritant properties and is not liable to change on exposure to the air. The following are the characters of the two substances of which it is composed, according to the German Pharmacopœia.

Paraffinum solidum.—A firm, white, odourless, microcrystalline substance obtained from inflammable minerals; melting at a temperature of 74° to 80° C. (165·2° to 194° F.).

Paraffinum liquidum.—A clear, colourless, oily liquid, obtained from petroleum, not fluorescent, free from taste or smell, having a specific gravity not lower than 0·880, and not vaporising below a temperature of 360° C. (680° F.).

Both compounds consist of neutral hydrocarbons, most of them belonging to the higher fatty series, C_nH_{2n+2}. They are found in geological strata, and are products of decomposition of large masses of animal matter.[1] From the same source we obtain—

Benzinum Petrolei, benzin. The colourless, non-fluorescent portions of petroleum, having a specific gravity of

[1] C. Engelr, 'Verhandl. d. Ges. deutschr. Naturf. u. Aerzte zu Bremen,' 1890, Bd. i, S. 129.

o·64 to o·67, and almost entirely distilling over at a temperature between 55° and 75° C. (132° and 167° F.). It has a strong, but not unpleasant odour, and is HIGHLY INFLAMMABLE. It consists of hydrocarbons of the fatty series, chiefly of C_6H_{14}, together with C_5H_{12} and C_7H_{16}, and their corresponding isomers. It is occasionally used as an anodyne liniment. On account of its strong poisonous effect on germs and low forms of organic life, it is sometimes given to check fermentation of the contents of the stomach, and as a remedy against worms;[1] it is also used externally in cutaneous disorders. The dose is from 10 to 30 drops. If administered soon after meat infected with trichinæ has been eaten, a few consecutive doses of 5 grammes each should be given; and these should be followed by an aperient powder. In a chemically pure state, and consequently free from empyreumatic products, its effects are not very harmful to human beings. In large doses it induces stupor.

LANOLIN is the name given to the purified fat of sheep's wool.[2] It chiefly consists of the ethers of palmitic and cerotic acid, and the alcohols known as Cholesterin and Iso-cholesterin, $C_{26}H_{43}(OH) + H_2O$, and is therefore not a true fat, as it does not contain glycerine, and consequently does not undergo saponification if treated with an alkali. When combined with water, lanolin is a whitish unctuous substance, having a faint odour and neutral reaction; it does not become rancid. It is insoluble in water, sparingly soluble in alcohol, but readily soluble in ether. If heated in a water-bath it melts and separates into two layers, the upper consisting of anhydrous, and the lower of hydrous lanolin. Lanolin is used either alone, or as a vehicle for other drugs. Its readiness to absorb water causes it to adhere to mucous membranes, and it may therefore be used to prolong the action of drugs upon these surfaces.

The crude fat of sheep's wool was called ŒSYPUS by the ancients, and was employed by them as a remedy, and also as a cosmetic, in the same way as lanolin is at the present day.

[1] A. Rey, 'Ref. Jahrbücher d. ges. Med.,' 1864, Bd. cxxii, S. 336; Mosler, 'Berl. klin. Wochenschr.,' 1864, S. 317.

[2] O. Liebreich, 'Berl. klin. Wochenschr.,' 1885, No. 47.

ICHTHYOL, a preparation containing sulphur, is an ammonium compound of ICHTHYOL-SULPHONIC ACID. It is a clear liquid of reddish-brown colour and syrupy consistence, with an empyreumatic odour and taste, and is soluble in water, alcohol, and ether. It is obtained by the distillation of peculiar fossil deposits, principally fish and aquatic animals, found in the Tyrol. The composition of the acid is stated to be $C_{28}H_{36}S_3O_6N_2$. It is highly recommended for internal and external use in cutaneous diseases[1] and in rheumatic and neurotic affections. As far as we know at present, ichthyol is not poisonous; it is generally diluted with oil (1 : 10) when applied as a liniment; as an internal remedy it is given in doses of from 15 to 20 drops.

GUMMI ARABICUM, gum arabic. Obtained chiefly from the *Acacia Senegal* (*Acacia verek*), which grows in Senegambia and the district about the upper Nile. It consists of slightly tinted and transparent tears or masses, which break up into angular fragments. It is soluble in two parts of water, insoluble in alcohol, and has a bland mucilaginous taste. It exudes, in the hot season, through the tissues of the stem and branches, or from incisions made in the bark of the trees, and is a variable compound of different gums, the chief of which is arabic acid ($C_{10}H_{18}O_9$?). If incinerated it leaves about 3 per cent. of ash, which is composed of the carbonates of calcium, potassium, and magnesium. In the intestine a portion is converted into sugar; the remainder is only very slowly transformed or absorbed, and in passing onwards retains its glutinous and protective character. It may be given either alone or as an emulsion with oil. The simplest way is to dissolve a teaspoonful of it in a glass of water, and in cases of intestinal catarrh to let the patient take the dose three or four times a day. As gum is not readily absorbed, its addition to other remedies may cause them to be retained longer in the stomach and intestinal canal, and thus render their local action more effective. Gum arabic possesses the property of retarding or preventing the precipitation of various chemical compounds, and of holding in suspension any precipitate which is formed. This

[1] P. Unna, 'Monatshefte f. prakt. Dermatol.,' 1882, S. 328,—the first of a series of treatises on the subject.

is a property which may sometimes be of value in dispensing certain remedies.

The preparations of gum arabic are—(1) MUCILAGO GUMMI ARABICI, mucilage of gum acacia, a simple solution of the gum in two parts of water. It is added to mixtures, in the proportion of 15—20 parts to 150, to enable the stomach to tolerate acrid or pungent substances. Mucilage which has been kept for some time, and become turbid, or in which, by the development of micro-organisms, free acids (lactic and acetic acid) have been formed, should not be used. (2) PULVIS GUMMOSUS, compound acacia powder, which consists of three parts of gum arabic, two of powdered liquorice root, and one of sugar.

RADIX ALTHÆÆ, marsh-mallow root. Obtained from *Althæa officinalis* (Malvaceæ), which grows wild in temperate climates. The roots, which are 2 dm. (8 inches) or more in length, and 1·5 cm. (half an inch) thick, when stripped of their yellowish-grey bark, are of a whitish colour externally, and are deeply furrowed longitudinally. They contain a large amount of vegetable mucilage, the composition of which, when dried at a temperature of 100° C., is $C_{12}H_{20}O_{10}$. The root has long been a popular remedy, as a sedative, in acute affections of the air-passages, as have also the officinal FOLIA ALTHÆÆ, marsh-mallow leaves, FOLIA MALVÆ, the leaves of *Malva vulgaris* and *Malva sylvestris*, and FLORES MALVÆ, the delicate blue flowers of *Malva sylvestris*. The preparations are—(1) SIRUPUS ALTHÆÆ, syrup of marsh-mallow; used as an addition to other mixtures. (2) SPECIES PECTORALES, which is prepared from Radix Althææ, Radix Liquiritiæ, Rhizoma Iridis, Folia Farfaræ, Flores Verbasci, and Fructus Anisi. Of this preparation marsh-mallow root forms the largest part. (3) SPECIES EMOLLIENTES, emollient herbs, prepared from Radix Althææ, Folia Malvæ, Herba Meliloti, Flores Chamomillæ, and Semina Lini.

As constituents of Species Pectorales we meet with the ancient remedies FOLIA FARFARÆ, or coltsfoot leaves, the leaves of *Tussilago farfara* (Compositæ), which grows wild in this country, and FLORES VERBASCI, or mullein, the flowers of *Verbascum phlomoides* and *Verbascum thapsiforme*. The latter are of a beautiful yellow colour. The HERBA MELILOTI,

melilot, a constituent of Species Emollientes, is obtained from *Melilota officinalis* and *M. altissimus*, Papilionaceæ growing in Germany. The drug has an aromatic odour, due to the presence of cumarin and a volatile oil.

TUBERA SALEP, salep or salep-root. The round or pear-shaped tubers of various orchids growing in Germany and the East. They are of a light brownish-grey or yellowish colour, hard and translucent, like horn. The chief constituent is a mucilage named bassorin. Like other kinds of vegetable mucilage, it swells up in water, and forms a glutinous mass which is not readily absorbed by the intestines. It is almost exclusively used as a remedy for intestinal catarrh, in the form of decoction (1—2 parts in 150 of water) with the addition of a little sugar. Tannin, which is often useful in the same disorder, though acting in a different manner, should not be combined with the decoction, since the tannin precipitates the bassorin. For the same reason, remedies containing tannin should not be administered simultaneously. In prescribing salep in infantile diarrhœa, the mistake — which is not uncommon — of supposing that it has any real nutritive value should be avoided. It contains nearly 28 per cent. of starch, 5 per cent. of albumen, and 1 per cent. of sugar (Dragendorff); the total amount of which, in the quantity used in making a thick decoction, must consequently be very small indeed. MUCILAGO SALEP, the officinal mucilage of salep, is a mixture of 1 part of salep with 10 of cold and 90 of boiling water. It should be freshly prepared each time it is prescribed.

Pliny[1] extols the virtues of orchis bulbs, saying that they stimulate sexual desire and cure ulceration of the mouth, catarrh of the air-passages, and—if taken in wine—diarrhœa. The first-named action of the orchis root, the shape of which is orchitic or testiculate, seems to be an idea which dominated the writer's imagination.

CARRAGEEN or Irish moss. The thallus of *Chondrus crispus* (*Fucus crispus*) and of *Gigartina mamillosa*, both algæ of the North Atlantic. It contains a large amount of mucilage (nearly 80 per cent.), as well as the saline constituents of sea water, but no starch. The algæ

[1] Plinius, 'Historia rer. natur.,' lib. xxvi, cap. 82.

dissolve completely in boiling water, with the exception of a little vegetable fibre, and the solution, if sufficiently concentrated, gelatinises on cooling. One gramme yields about 25 grammes of jelly. Probably it is from the appearance of the jelly, which somewhat resembles that of coagulated albumen, that various medical men have attributed great nutritive value to carrageen.

It is a useful remedy in irritable conditions of the intestinal canal; its efficacy in affections of the air-passages is not very pronounced. It is given as a decoction of 5 to 10 parts in 300 of water.

Lycopodium, Semen Lycopodii, or lycopodium spores. A pale yellow and very mobile powder, without taste or smell, obtained from *Lycopodium clavatum*, a cryptogamous plant growing in Northern and Central Europe. The fructification consists of little, uniform capsules containing numerous bright yellow spores. The latter have a fatty envelope which makes the powder unctuous to the touch, and renders it slightly adherent to the skin; the spores contain fatty oil, mucilaginous extract, and other inactive constituents. Under the microscope the spores present the appearance of granules of almost equal size, with one arched and three fairly flat surfaces. Lycopodium has been recommended as an internal remedy in irritable conditions of the urinary organs, given as an infusion of 10 parts in 150 of water. It can be made into an emulsion with mucilage of acacia. Externally, lycopodium may be usefully employed as a dusting powder to excoriated surfaces, as in intertrigo of the nates, mammæ, or groin, and in eczema, erysipelas, &c. For this purpose it may be advantageously combined with a tenth part of finely powdered oxide of zinc.

It is also used for enveloping pills in order to prevent their adhesion.

An important place among fatty oils must be assigned to Oleum Jecoris Aselli, cod-liver oil. It is obtained by various processes, in Norway and Newfoundland, from the liver of *Gadus morrhua* (*Asellus major*, or true cod) and other species of the Gadus family. The clearest oil is that which is allowed to drain from the fresh livers, piled one upon

another. That which is officinal in Germany is obtained by placing the incised livers in a vapour-bath at a gentle heat. It should be pale yellow, free from any rancid taste or smell, and should have a slightly acid reaction.

Cod-liver oil consists of about 70 per cent. of olein and upwards of 25 per cent. of palmitin, but it contains very little stearin, and on this account does not become turbid when cooled down to the freezing-point of water. It also contains free oleic, palmitic, and stearic acids, as well as some volatile acids to which its odour is due; together with traces of various biliary principles and marine salts, both of which, however, being insoluble in fat, are gradually precipitated.

Cod-liver oil has long been popularly employed in Northern Europe, especially in rheumatic disorders. It was first brought to the notice of the profession as a remedy for chronic rheumatism in 1782 by T. Percival, of Manchester, but it was not until the publication of an important treatise by Professor Bennett,[1] of Edinburgh, that it came into general notice. It appears that it was formerly a popular remedy in Germany, and especially in the Rhenish and neighbouring provinces. The dark offensive oil was used then, as it is still, in the manufacture of leather, and patients obtained from the tanneries what they required either for internal or external use. In 1822 Schenck,[2] the district physician in Siegen, published[3] his 'Experiences of the Great Curative Powers of Cod-liver Oil,' the statements in which were confirmed in 1824 by Günther,[4] of Cologne. From that time favourable reports as to its action were continuously forthcoming. Schenck's wish that cod-liver oil should be included in the Pharmacopœia was granted, and the remedy has been retained in every subsequent edition.

Cod-liver oil very often increases the nutritive powers,

[1] J. Hughes Bennett, 'Treatise on the Cod-liver Oil as a Therapeutic Agent in Gout, Rheumatismus, and Scrofula,' London, 1841, 180 pp.

[2] Not Scherer, as the name is erroneously spelt in the title of the paper.

[3] Schenck, 'Journ. d. prakt. Heilkunde,' Bd. lv, St. 6, S. 31—58.

[4] Günther, ibid., Bd. lviii, St. 8, S. 111.

and causes a marked change for the better in chronic disorders, such as rheumatism, paralysis, scrofula, and incipient tuberculosis. In such maladies the change is probably entirely due to the improved nutrition of the patient; we have, at least, no reason to ascribe to the remedy any specific—that is to say, any direct—action upon the cause of the disease. It was at first supposed that some effect of this kind might be produced by the iodine contained in the oil, but the amount (about 0·04 per cent. combined with soda or some other base) is quite insufficient for any such purpose. It was then maintained that cod-liver oil was nothing but a fat, and that other fats must produce the same results; a theory disproved by the simple fact that the same quantity of other fats cannot be tolerated by the stomach and intestine.

Upon this point certain experiments have been made.[1] A healthy man of thirty years of age took daily from 30 to 60 grammes (about 1 to 2 ounces) of the various fatty foods in common use, his diet being in other respects of a uniform character. It was then determined how much of the fat passed off each day in the fæces, and how long a period elapsed before the organism was saturated with fat, and consequently excreted almost the whole amount taken. With vegetable fats this occurred in twelve days; with butter, in a month; with the pale, decolourised cod-liver oil also in a month; and the period was certainly longer than a month with pure brown cod-liver oil. The experimenter arrived at the conclusion that olive oil, poppy and almond oils should be classed as substances digested with difficulty, whale oil and colourless cod-liver oil as digestible, and brown cod-liver oil as easily digestible. In the case of vegetable fats this observation is confirmed by experience, for, when given to the same extent as cod-liver oil usually is, they occasion diarrhœa.

Why is it that cod-liver oil is more easily digested than other kinds of fat? Its digestibility was attributed,[2] in the first place, to the fact that fish oil is more readily absorbed by animal membranes, both in the dry and recent state, than

[1] Berthé, 'Gaz. méd. de Paris,' 1856, p. 323 (Compt. Rend.).

[2] O. Naumann, 'Arch. d. Heilkunde,' 1865, Bd. vi, S. 536.

any other fatty oils, and that with dark cod-liver oil this takes place to an exceptionally large extent; it was further suggested that as, owing to the presence of the bile acids in the oil, capillary attraction is intensified, so their presence also intensifies the absorption of the oil in the alimentary canal. To this explanation, however, objections have been advanced[1] which, so far as I am aware, have not yet been met; the chief objection is that clear cod-liver oil contains no biliary constituents whatever, as, with the exception of cholesterin, they are insoluble in fatty oils. The explanation probably rests upon other grounds, which have only been advanced within a comparatively recent period.[2]

Cod-liver oil differs from most other fatty oils in containing free fatty acids, which amount in the dark kinds to about 5 per cent., and in the light to considerably less. It can be emulsified much more readily than other oils,—that is, it can be subdivided into extremely minute globules, each enveloped with a covering which keeps them separate, and in this minutely divided state the oil can be easily absorbed by the lacteals in the intestine. Here is an illustration:

In these two tubes I have a weak solution of carbonate of sodium, corresponding with the alkaline reaction of the secretion in the small intestine. To the solutions I add a little pure olive oil, and to one of them I also add some free oleic acid, and I then agitate both tubes thoroughly and equally. The contents have now become milky, but in one the oil will, in the course of an hour, be floating on the surface; in the other, containing the free acid, this does not take place till much later. Thus we see that the agitation has separated the neutral oil into large drops which quickly coalesce; but the acidified oil has thereby assumed the consistency of milk.

The objection, however, may be raised that in the intes-

[1] Buchheim, 'Arch. f. exper. Path. u. Pharm.,' 1874, Bd. iii, S. 118.

[2] E. Brücke, 'Die physiol. Bedeutung d. teilw. Zerlegung der Fette im Dünndarm, Sitzungsbr. Akad. d. Wiss. Wien,' 1870, Bd. lxi, Abth. 2, S. 362; J. Gad, "Zur Lehre von der Fettresorption" 'Arch. f. Anat. u. Physiol.,' 1878, Physiol. Abth., S. 181; G. Quincke, "Ueber Emulsionsbildung," u. s. w., 'Arch. f. d. ges. Physiol.,' 1879, Bd. xix, S. 129.

tines there is no action corresponding with the agitation in the test-tube or with other physical methods by which emulsions are prepared in the laboratory. How then can such a result be effected in the intestines?

If in a watch-glass, a drop of acidified oil is allowed to float quietly on the surface of a weak solution of soda, the oil is very soon invested with a white film of soap, and is then surrounded with a whitish turbid ring, which grows larger at the expense of the oil. If the process is watched under the microscope with a low power, the part around the oil drop is seen in most active movement, the tiny particles in the turbid area forming a series of eddies around the drop. Under a higher power the particles are seen to be minute fatty globules of uniform size; saponification takes place, and results in the separation of the fatty globules and causes their circulatory movement; every globule of oil is coated over with soap, and a minutely divided and uniform emulsion is the result.

Cod-liver oil is well adapted for this experiment. The acid already exists in it which, combining with the alkaline secretion of the intestine, forms the emulsifying soap, and consequently has not to be separated from the fatty oil by the action of the pancreatic juice. It is evident, therefore, that the oil can be very easily emulsified, that it arrives in the intestine under conditions which are highly favourable to its minute subdivision, and that it consequently is absorbed into the circulation more rapidly than other fats. These results will be more distinctly manifested when, owing to some morbid change in the parts, the ordinary process of digestion is enfeebled. The intestine, being relieved of part of its work, is assisted in furnishing the normal supply of fatty matter to the blood. The emulsifying process is promoted by the presence of sodium chloride and of bile.

This explanation cannot be regarded as perfectly complete. Attention has been drawn to the fact that several substances are present in cod-liver oil which might reasonably be expected to produce special effects. No other animal fat contains, even approximately, the same amount of cholesterin,[1] a substance which is unquestionably associated with

[1] E. Salkowski, 'Therap. Monatshefte,' 1888, S. 230.

cell development, being a constituent of the young and most vigorous cells both of plants and animals. Bases of a special kind have been found in cod-liver oil,[1] and the question very naturally arises, Is not the digestion of the oil as well as its absorption and assimilation materially influenced by the presence of these constituents ?

During infancy, or when there is a disordered state of the stomach or bowels, or an invincible repugnance to the remedy, also in hot weather, cod-liver oil disagrees and its use is contra-indicated ; even when none of the above conditions exist, it is often necessary gradually to accustom the patient to its use. In such cases any other fat in the same quantities would be tolerated even less readily, with the exception possibly of fresh butter, which may be emulsified in the mouth if thoroughly masticated with stale, well-aërated bread. Taken in this way, butter is perhaps the best and most agreeable substitute for cod-liver oil.

The daily dose of cod-liver oil is from half a teaspoonful to four tablespoonfuls at the most, varying according to the age of the patient. If desired, some aromatic wine may be taken after the dose.

Based on the assumption that the greater digestibility of cod-liver oil is due to the presence in it of the free fatty acids, v. Mering[2] has proposed to substitute for it a mixture of pure olive oil, with 6 per cent. of liquid oleic acid. To this preparation he has given the name of *Lipanin*. The advantages which it possesses are its freedom from the characteristic smell and taste of cod-liver oil, which some patients cannot tolerate, and the uniform amount of fatty acid contained in it. Favourable reports as to the action of this compound have from time to time been published.

SESAMUM OIL, Benné oil, has lately, on the same grounds, been highly recommended by C. von Noorden. This oil was known to the early Persians and Egyptians, and is esteemed by the modern Arabs and other people of the East as a food and as an external application to promote softness of the skin. It is laxative in large doses.

[1] A. Gautier and L. Mourgues, 'Compt. rend. de l'Acad. des Sc.,' 1888, vol. cvii, pp. 110, 626, 740.

[2] v. Mering, 'Therap. Monatshefte,' 1888, S. 49 u. 233.

XXX.

Cutaneous irritants—Theories with regard to their action—Brine baths (Mutterlaugen) and salts—Formic acid—Cantharides—Oil of mustard—Pyrogallic acid—Chrysarobin—Inorganic acids, bases, and salts.

CUTANEOUS IRRITANTS are very freely used, and results of the most diverse character are expected from them. They are locally applied to promote the absorption of exudations seated beneath a sound part; they are intended to divert, or draw away either the cause of disease, or the results produced by disease, from one part of the body to another; hence the names Derivative and Epispastic (from ἐπισπάω = I draw on, allure). They are supposed to modify, by reflex action, the circulation, the metabolism, and the various processes which result from the activity of the nervous centres.

Before applying active cutaneous irritants such as blisters, especially over a large surface, the question should invariably be considered, whether another very painful and perhaps useless disease may not thereby be added to that which already exists. The beneficial change in the patient following the application of these remedies has not unfrequently been attributed to the action of the remedy, for the simple reason that the change was *post hoc ergo propter hoc.* Since the practice, however, has been abandoned in Germany of applying counter-irritation to the whole of the abdomen in peritonitis, or to the entire side of the chest in pleurisy, &c., the results of treatment have not been worse, whereas the patient himself has experienced decidedly less discomfort.

The reflex nervous action of irritants, when applied externally, has been studied on frogs, bats, and on the human subject,[1] and certain conclusions have been arrived

[1] O. Naumann, 'Archiv f. d. ges. Physiol.,' 1872, Bd. v, S. 196; L. Jacobson, 'Arch. f. path. Anat.,' 1876, Bd. lxvii, S. 166.

at, which have reference chiefly to the effect on the heart and cutaneous vessels. Of the therapeutic effects of the changes in these organs, resulting from the action of slight or severe cutaneous irritation, we as yet know nothing.

The following conclusions were drawn from experiments[1] performed on rabbits.

Cutaneous irritants, among which warm brine and sea-water baths must be included, stimulate the central reflex apparatus, and thus cause more active metabolism, manifested by an increased consumption of oxygen and an increased elimination of carbonic acid. The same results are produced by cooling the surface of the body. It is in the muscles that the greater part of the metabolic changes takes place, and it is in them that the metabolic changes are most largely influenced by alternations of temperature (and probably also by the irritant action of saline baths). Sinapisms applied to rabbits increased the consumption of oxygen and the elimination of carbonic acid, in a similar fashion. An ordinary bath of warm water, saturated with carbonic acid, does not produce this effect.[2]

If a concentrated solution of chloral hydrate is slowly rubbed into the skin of the abdomen of a warm-blooded animal, it should, according to Brown-Séquard, by reflex action, produce changes in the circulatory apparatus; but when the experiment was tried, no changes were observed.[3] Neither was any apparent change produced when nitric, acetic, and formic acids were applied in a caustic form, so as to cause slight manifestations of pain; the blood-pressure was unchanged, and there was no evidence in any of the nervous centres of any reflex phenomena.

The cutaneous irritants derived from the inorganic kingdom are not included in the Pharmacopœia. They are the saline constituents of sea water and of mineral waters, a detailed account of which belongs to the department of balneology. As they all probably have a similar and uniform action I will here only refer more particularly

[1] Röhrig und Zuntz, 'Arch. f. d. ges. Physiol.,' 1871, Bd. iv, S. 57.

[2] F. Paalzow, 'Arch. f. d. ges. Physiol.,' 1871, Bd. iv, S. 492; Röhrig, 'Deutsche Klinik.,' 1873, No. 23.

[3] L. Schulz, 'Arch. f. exper. Path. u. Pharmakol.,' 1883, Bd. xvi, S. 310.

to the well-known brine or mother liquor (Mutterlauge) of the springs of Kreuznach, Rehme, Soden, &c.[1] It is the residue left in the salt-pans after allowing the water from the spring to evaporate for several days and after the sodium chloride has been deposited. When the latter has been removed there remains a clear, brownish-yellow liquid of an oily consistency, containing from 32 to 35 per cent. of saline matter, the greater part of which is calcium chloride, together with small quantities of other chlorides. The bromides, which are present in much smaller amounts, and the iodides, of which there is merely a trace, need not be taken into consideration. The salt obtained by evaporating the brine to dryness is known commercially as Mutterlaugensalz. Here is the analysis of the Kreuznach brine (Mutterlauge) according to Aschoff, 1000 parts of which contain—

Contents.	Theodorshalle.	Munster am Stein.
Calcium chloride	256,775	243,280
Magnesium chloride	21,912	28,462
Strontium chloride	8,585	9,953
Potassium chloride	29,710	29,145
Sodium chloride	21,153	23,680
Bromide of magnesium	7,650	7,664
Iodide of magnesium	0,009	0,009
Lithium chloride	4,847	4,410
Cæsium chloride and rubidium	Traces	Traces
Total	350,641	346,603
Specific gravity	1·3348	1·3314

During the bath the salts are not absorbed by the skin;[2] they simply produce a general stimulating effect on the surface of the body, which is manifested by reddening of the skin. Whether calcium chloride possesses special

[1] Heusner, 'Berl. klin. Wochenschr.,' 1888, No. 30; E. Lier, 'Monatshefte f. prakt. Dermatol.,' 1888, Bd. vii, No. 8.

[2] With regard to this much-debated question reference may be made to the following:—R. Winternitz, 'Arch. f. exper. Path. u. Pharmak.,' 1891, Bd. xxviii, S. 405; Paschkis und Obermayer, 'Cbl. f. klin. Med.,' 1891, S. 65, as well as to the works referred to in the lecture on potassium iodide.

irritant properties or not, is unknown. Till this has been demonstrated, the bath may be prepared with ordinary coarse salt, which has the advantage of being much cheaper, and if added in sufficient quantity, causes a similar reddening of the skin. From 1 to 5 litres of the Kreuznach Mutterlauge should be added to a full bath, or the same number of pounds of the Kreuznach salt, or of common salt, according to the size of the bath, the age of the patient, and the sensitiveness of the skin. The proper proportion is perhaps that of sea-water, the saline constituents of which amount to nearly 4 per cent., three fourths being sodium chloride (the water of the Baltic at Kiel contains only 1·77 per cent. of salts, with 1·49 per cent. of sodium chloride).

Cutaneous irritants belonging to the organic kingdom are largely represented in the Pharmacopœia; of these I will first discuss two acid substances, Formic Acid and Cantharidin.

Acidum Formicum, formic acid, H.COOH, is a clear, colourless, and volatile liquid, with a pungent odour and a strong acid taste, and is generally prepared by heating oxalic acid in contact with glycerine. The officinal preparation contains about 25 per cent. of real acid, and 75 per cent. of water. Four parts of it, mixed with 70 of alcohol and 26 of water, constitute the Spiritus Formicarum, which is employed as a counter-irritant in neuralgia and rheumatism. Decoctions of living ants were formerly used; formic acid, as is well known, being secreted by the female ants from glands which open on the surface of their bodies. In addition to humic acid, ferrous and other sulphates, formic acid is one of the constituents of mud or peat baths.[1]

Formic acid, owing to its action on micro-organisms, is very effective in checking fermentation and putrefaction.[2] It is possible that this property may be one cause why preparations containing it act beneficially in cutaneous disorders.

Formaldehydum Solutum, solution of formic aldehyde, H.COH. in water, has only been recently introduced as a

[1] G. Loimann, 'Therap. Monatshefte,' 1891, S. 344.

[2] K. Müllenhof, 'Tagebl. d. Versamml. d. Naturf. u. Aerzte,' Magdeburg, 1884, S. 175; H. Schulz, 'Deutsche med. Wochenschr.,' 1885, S. 410.

therapeutic agent. It is a clear, colourless, watery liquid, with a pungent odour, and has a neutral or very slightly acid reaction. The specific gravity is 1·079—1·081. The solution contains about 35 per cent. of formic aldehyde. It is miscible in all proportions with water and alcohol, but not with ether. It has frequently been recommended as a strong antiseptic. Upon micro-organisms it acts as a powerful poison,[1] and is therefore peculiarly adapted, in the form of a 1 per cent. solution, for cleansing and preserving sponges, and as a wash for the hands and for instruments. It has a tanning and mummifying action upon the skin. There is a powder sold under the name of Formalith, which consists of a mixture of formalin and silicious earth.

A remedy handed down from ancient times[2] is—

CANTHARIDES, Spanish flies, or blistering flies.—Coleoptera which are found both in Northern countries, where the elytra or wing-sheaths are of a coppery-green colour, and in Southern districts, where the elytra have a blue iridescent colour. The beetles are from 15 to 30 mm. in length, and from 6 to 8 mm. broad, and have a strong, disagreeable odour. Their irritant action upon the skin is due to cantharidin, $C_{10}H_{12}O_4$, a white crystalline substance. It is an anhydrous acid, which, by absorption of one molecule of water, is converted into a dibasic acid, and with alkalies, forms salts. If taken internally or subcutaneously injected it produces acute inflammation of the stomach and intestines, and especially of the urinary organs.[3] It is soluble in fatty oils, and to this property it owes its efficacy when used in the form of plaster. The cantharidin dissolves in the oil (the mass is not chemically a plaster, but a compound of oil, wax, and turpentine), and by irritating the skin causes serous exudation, and develops a blister. The plaster when applied to the nape of the neck, or even the rubbing in

[1] O. Loew, 'Berichte d. Münchener chem. Ges.,' 1888; Berlioz und Trillat, 'Comptes rendus,' Paris, 1892, vol. cxl, p. 290; H. Aronsohn, 'Berl. klin. Wochenschr.,' 1892, S. 749.

[2] Dioscorides, lib. ii, cap. 65.

[3] "Rundes Magengeschwür und Schrumpfniere bei Tieren infolge subcutaner Einspritzungen von Cantharidin," Aufrecht, 'Cbl. f. d. med. Wissensch.,' 1882, S. 545 und 849.

of an oleaginous solution of 1 in 4 of cantharides, causes first of all dilatation of the vessels of the pia mater, and then considerable contraction, the contraction remaining for some time.[1]

There are two forms of cantharides plaster, the EMPL. C. ORDINARIUM and the EMPL. C. PERPETUUM. The only essential difference between them consists in the amount of cantharidin, and in the latter containing gum-resin, EUPHORBIUM, a yellowish exudation from the African *Euphorbia resinifera*. The Empl. ordinarium generally raises a blister in the course of ten or fifteen hours, whereas the Empl. perpetuum does so only after several days, and even then sometimes merely reddens the skin. To keep up suppuration from a blistered surface the UNGUENTUM CANTHARIDUM is used. This is a mixture of the oily extract of cantharides (officinal under the name of Oleum Cantharidatum) and wax, and has a yellow appearance. It is very important to bear in mind that inflammation of the kidneys and bladder is apt to follow the application of the plaster,[2] and may be still more readily induced by the use of the ointment.

UNGUENTUM CANTHARIDUM PRO USU VETERINARIO is an extract of cantharides in olive oil, with the addition of wax, turpentine, and euphorbium. It is a greenish-black ointment.

Cantharides are also employed internally, both in the form of powder and of TINCTURA CANTHARIDUM. The dose of the tincture[3] is from 0·05 to 0·5 (!) gramme ($\frac{3}{4}$ to $7\frac{1}{2}$ minims); of the powder from 0·005 to 0·05 (!) gramme ($\frac{1}{12}$ to $\frac{3}{4}$ of a grain). The remedy should always be given in mucilage to prevent any irritation of the stomach or intestines. On account of the risk there is of this remedy acting injuriously upon the kidneys, it is very necessary to be extremely cautious with regard to its administration. It has been recommended as a diuretic, and also as a stimulant in enfeebled conditions of the male generative organs and of the bladder. The reason of this was, that in poisoning from

[1] Mosler, 'Deutsche med. Wochenschr.,' 1878, S. 305.

[2] R. Demme, 'Bericht über das Kinderhospital zu Bern,' 1887, S. 39.

[3] The German tincture is eight times the strength of the Tinctura Cantharadis, Ph. B. [Transl.].

cantharides, violent erections, amounting to priapism, took place, and it was supposed that moderate doses would produce the same effect in a lesser degree. This at an early period led to powdered cantharides being regarded as an aphrodisiac; it was a common ingredient of "love philtres" (Philtra), and as such played a notorious part in France and other countries in the last century.

The cutaneous irritant in most frequent use is the mustard poultice, which is prepared from SEMEN SINAPIS, black mustard seed, the seed of *Brassica nigra*, an indigenous plant belonging to the Nat. Ord. Cruciferæ. When chewed, it has at first a mild, oily, and slightly acid flavour, which soon becomes of a very pungent character, owing to the development of oil of mustard. Under the influence of the warm saliva the myronate of potassium contained in the seeds is rapidly converted, by a ferment which they also contain, into potassium bisulphate, sugar, and ethereal oil of mustard or allyl sulphocyanide.

$$KC_{10}H_8NS_2O_{10} = KHSO_4 + C_6H_{12}O_6 + C_3H_5.SCN.$$

The same decomposition takes place in preparing a mustard poultice or sinapism. To 150 or 200 grammes (5 to 7 ounces) of pounded mustard seed as much lukewarm water is added as will form a stiff paste; this is thinly spread upon linen and laid upon the unbroken skin, either directly or, better still, with some thin material intervening. The poultice is now covered over and left in contact with the skin till the patient experiences an unpleasant burning sensation. This occurs after an interval varying, according to the strength of the sinapism and the susceptibility of the skin, from ten minutes to three quarters of an hour. The reddened part is then wiped and dried with a soft sponge or towel.

If the officinal ethereal OLEUM SINAPIS is used, a piece of blotting-paper may be moistened with Spiritus Sinapis, which consists of 1 part of the oil to 49 of rectified spirit, and then laid evenly on the skin and covered with some material such as oiled silk, which prevents rapid evaporation. The CHARTA SINAPISATA, or mustard leaf, is a milder application. This is a paper coated with a mixture of mustard powder, from which the fixed oil has been ex-

tracted by percolation with benzin, and solution of gutta percha. The coating should be free from rancid smell, and should adhere firmly to the paper. If the leaf be moistened with water a strong odour of ethereal oil of mustard should immediately be developed.

Ethereal oil of mustard possesses another property, which may possibly be of service when the oil is applied externally; it is highly destructive to parasitic micro-organisms. Its power of preventing the disintegrating action of these organisms approximates to that of the best inorganic antiseptics; whereas it has scarcely any effect upon the unorganised ferments in the bodies of living animals.[1] Oil of mustard is also capable of permeating through the outer skin; these two facts may, therefore, offer some explanation of the resolvent action of sinapisms, when frequently repeated, on many swellings and tumours. The same facts may perhaps explain the cure or improvement resulting from the use of warm mustard baths, or from the internal administration of oil of mustard, in fevers, like malaria, for example, due to parasitic organisms.

An oil closely resembling the foregoing, and consisting mainly of butyl sulphocyanide, $C_4H_9.SCN$, or butyl isothiocyanate, is contained in HERBA COCHLEARIA, the *Cochlearia officinalis*, scurvy-grass, belonging to the Nat. Ord. Cruciferæ, and growing on the coasts of Northern Europe, and in the neighbourhood of the saline springs of Central Europe. The fresh plant, when in blossom, is cut in pieces and distilled with alcohol and water. The result is a clear, colourless liquid which has a peculiar odour, and a pungent, bitter taste. In former times, spirit of scurvy-grass was often used in scorbutic affections, as an addition (in the proportion of 1 in 10) to lotions or washes for the mouth. The plant was first introduced as a medicine by Johann Weyer.[2] He

[1] R. Henze, 'Das ätherische Senföl,' Doctordiss., Halle, 1878; Th. Haberkorn, 'Das Verhalten von Harnbakterien gegen Antiseptica,' Doctordiss., Dorpat, 1879 (see the preface); J. Wernitz, 'Ueber die Wirkung d. Antiseptica auf ungeformte Fermente,' Doctordiss., Dorpat, 1880; R. Koch, Mitteilungen aus dem kaiserlichen Gesundheitsamte,' Berlin, 1881, Bd. i, S. 271.

[2] C. Binz, 'Johann Weyer, a Rhenish Physician, the First Opponent of Witchcraft,' Bonn, 2nd edition, 1896.

published a description of it[1] with illustrations, and recommended its employment in scurvy.

We may also include here Flores Arnicæ, arnica blossoms. These are the flowering heads of *Arnica montana*, Nat. Ord. Compositæ, which grows wild in Germany. They contain ethereal oil and an amorphous acid, and were formerly largely prescribed for paralytic and other affections.[2] From these the Tinctura Arnicæ is prepared, which is chiefly employed as a resolvent liniment. It is, however, a stronger irritant than is generally supposed. The alcoholic extract of the fresh blossoms, treated with chloroform, yields, after the chloroform has evaporated, a greenish-yellow substance, the irritant action of which, when applied to the healthy skin, is strong enough to raise a blister.

The poisonous properties of the flower and root of *Arnica montana* have been demonstrated both upon individuals[3] and upon animals.[4]

[1] J. Weyer, 'Artzney-Buch: Von etlichen biss anher vnbekannten vnd vnbeschriebenen Kranckheiten,' Frankfurt-a.-M., 1583, S. 1—27.

[2] Arnica may claim a classic reputation as having apparently cured Goethe of a severe pulmonary affection. Eckermann, in his 'Gespräche mit Goethe,' Leipzig, 1876, Teil iii, S. 10, writes:

"Thursday, February 24th, 1824.—A very anxious day as regards Goethe, no improvement setting in at noon, as was the case yesterday. During a paroxysm of faintness he said to his daughter-in-law, 'I feel that the moment has come when I have to struggle between life and death.' Nevertheless in the evening the patient was fully conscious, and even in exuberant spirits. 'You are too timid with your medicines,' he said to Rehbein, 'you treat me too tenderly! When you have such a patient as I am to deal with, you should proceed in a somewhat Napoleonic fashion.' He then drank a cupful of a decoction of arnica, which, administered by Huschke yesterday at a critical moment, had brought about the favourable crisis. Goethe made a graceful allusion to the plant, and extolled its powerful efficacy to the skies. . . . At one period, when he seemed better, his chest being easier, his mind clear, and he was talking freely, Rehbein whispered to one of the bystanders, 'A freer respiration is generally associated with a fuller inspiration.' Goethe, who overheard, cried with great hilarity, 'That is a truth I have long known; but it does not apply to you, you rogues!'"

[3] Jörg, loc. cit., S. 132.

[4] Viborg, in Wibmer, Bd. i, S. 231.

Large doses set up local irritation of the stomach and intestines, and induce paralysis of the nervous centres.

Several cases of arnica poisoning have been reported in the medical journals;[1] one, which ended fatally and is little known, I will briefly relate to you.[2]

A pint bottle filled with tincture of arnica, instead of brandy, was given to a person who habitually indulged in spirituous liquors, as a practical joke. According to the evidence given at the official investigation, he probably drank from 60 to 80 grammes (15 to 20 drachms) of the tincture. Immediately afterwards he complained of the pungent taste of the liquid, and of severe burning pain in the stomach. On the following day the pain continued, but the patient was still able to go about. At 2 o'clock in the night, however, the pain become more violent; about 9 in the morning the patient tried to rise from his seat, but fell to the ground, breathed heavily, and died. This occurred thirty-eight hours after swallowing the tincture. At the post-mortem examination the stomach and intestines were found to be inflamed.

In my own laboratory I directed some investigations[3] to be made with regard to the action of this plant, a point upon which little attention has been bestowed. The results were the same as those above mentioned. The alcoholic extract of arnica flowers, however, completely loses its poisonous action by being kept for a few weeks.

Fructus Capsici, capsicum, Spanish pepper. The conical red fruit of *Capsicum annuum*, a plant belonging to the Nat. Ord. Solanaceæ, which is cultivated in Germany for ornamental purposes. From the fruit an oily, reddish-brown liquid can be extracted which has a pungent taste, and if applied to the skin excites intense burning pain and inflammation. The fruit is said to stimulate the action of the kidneys, and to increase the secretion of urine. By veterinary surgeons it

[1] H. Bertin, 'Lancet,' 1864, Bd. ii, p. 571; A. Schumann, 'Jahrb. d. ges. Med.,' 1868, Bd. cxl, S. 264.

[2] Wilms, 'Verhandl. d. Naturhist. Ver. f. Rheinl. u. Westfalen,' 1873, S. 48.

[3] W. Wilckinghoff, 'Medic. Beiträge zur Kenntniss der Arnica montana,' Doctordiss., Bonn, 1880.

is employed as a cutaneous irritant, and also to excite sexual desire; in cookery it is used as a pungent seasoning. The extract (capsicol), obtained by means of benzin, when applied to the mucous membrane of the stomach of a dog with a gastric fistula, induced slight redness and immediate secretion of gastric juice. The same effect took place when capsicol was merely applied to the tongue.[1] TINCTURA CAPSICI, added to other preparations, is sometimes used as an external application to prevent the hair from falling out.

The two following remedies belong to the aromatic series, and have only recently been recommended for use by the dermatologists.

PYROGALLOLUM, pyrogallic acid, or trihydroxyl-benzol, $C_6H_3(OH)_3$. It consists of white, brilliant scales or needles having a bitter taste, and forming with three parts of water a clear, colourless, and neutral solution. The acid is also soluble in alcohol and ether. If caustic soda be added to the aqueous solution it quickly turns brown.

Pyrogallic acid is produced by the action of heat on gallic acid; it does not form salts, and is, in fact, not an acid. It is used with advantage for the cure of scaly eruptions, and also in cases of lupus, &c. It has a caustic action, which is due to its strong reducing or deoxidising power. In this alkaline solution of pyrogallic acid you see that the brown discoloration, of which I have spoken, begins distinctly at the surface, and spreads rapidly downwards. On the addition of $AgNO_3$ to a solution which is not alkaline, it instantly becomes grey and turbid from the precipitation of the silver. Both are the results of the rapid absorption of oxygen by the pyrogallic acid.

One way, among others, in which it may be used is by freely applying a solution of 5 to 10 parts in 100 of rectified spirit, to the diseased skin, every day by means of a brush made of bristles; but never to any large extent of surface at once, as, if absorbed, it may readily prove fatal by destroying the blood-corpuscles, decolourising the blood, and causing obstruction of the uriniferous tubules with pigment

[1] A. Högyes, 'Arch. f. exper. Path. u. Pharmakol.,' 1878, Bd. ix, S. 117.

casts.[1] It is also used, mixed with 10 parts of vaseline, as an ointment. As a general rule, small doses of pyrogallic acid are readily borne even when the amount given is sufficient to pass unchanged in the urine.

CHRYSAROBINUM, $C_{30}H_{26}O_7$, the active principle of Goa powder, is a light yellow crystalline powder obtained by purifying the Goa powder found in irregular interspaces in the wood of the *Andira araroba*, a plant belonging to the Nat. Ord. Leguminosæ, and growing in Brazil. When boiled in 2000 parts of water, chrysarobin, without absolutely dissolving, yields a tasteless filtrate of faint reddish-brown tint, which does not change the colour of litmus paper.

Applied to the healthy skin, chrysarobin induces an inflamed condition which often extends far beyond the spot to which it is applied. If cautiously employed in the form of an ointment or wash, it cures cutaneous disorders of a scaly or parasitic character. It produces a temporary discoloration of the skin, of a reddish-brown or violet appearance, the latter especially if soap is used after the chrysarobin. When acted upon by an alkali, chrysarobin combines with oxygen to form 2 molecules of chrysophanic acid, $C_{15}H_{10}O_4$, and 3 of water: $C_{30}H_{26}O_7+4O=3H_2O+2C_{15}H_{10}O_4$. This change is also produced when chrysarobin is absorbed into the system, or even when a mixture of it with fat or vaseline is applied externally. Any portion of the chrysarobin which reaches the kidneys without being decomposed may there give rise to inflammation and albuminuria. In alkaline urine the resulting chrysophanic acid manifests its presence by producing a reddish colour similar to that caused by rhubarb.[2] Chrysophanic acid is a derivative of benzol, and allied to anthracene ($C_{14}H_{10}$), a constituent of coal-tar.

Hydrochlorate of HYDROXYLAMINE has proved of equal efficacy with the two previous remedies in the treatment of acute cutaneous disorders, and further has the advantage of not causing, as they do, any discoloration of the skin or of the linen. It consists of transparent, colourless crystals

[1] G. Jüdell, Hoppe Seyler's 'Med.-chem. Unters.,' 1868, S. 422; J. Personne, 'Compt. rend. de l'Acad. des Scienc.,' 1869, Bd. lxix, S. 749.

[2] A. Lewin u. O. Rosenthal, 'Arch. f. pathol. Anat.,' 1881, Bd. lxxxv, S. 118.

which have an acid reaction, and are readily soluble in water. The composition of hydroxylamine is $NH_2.OH$. It may be obtained by treating nitric acid with nascent hydrogen, or more easily by treating mercuric fulminate with strong hydrochloric acid. It is a very powerful reducing agent, and is consequently poisonous if taken internally, inducing profound narcosis and the formation of methæmoglobin.[1] It has been used externally in solutions of 1 in 1000, without producing any injurious effects.

Among the caustic remedies to which I have not yet referred are—

Acidum Chromicum, chromic acid, CrO_3, which consists of crimson-red crystals, which are very deliquescent, and readily soluble in water. Its caustic action is due to the evolution of nascent oxygen, the acid being thereby converted into green chromic oxide, $2CrO_3 = Cr_2O_3 + 3O$. If heated, the crystals of chromic acid acquire a deeper colour, and then liquefy and give off oxygen. When heated with hydrochloric acid, chlorine is liberated. A 3 per cent. solution of chromic acid applied with a brush will generally cure excessive sweating of the feet.

In exceptional cases, a continuous itching and smarting may be set up after the application; this can be relieved in some measure by the use of salicylic ointment. Small fissures, chaps, or ulcers of the skin are also sometimes developed. If chromic acid is inadvertently applied to superficial abrasions of the feet, it produces swelling and sometimes eczema of the lower part of the leg, or even inflammation of the lymphatic vessels and glands. Among other unpleasant results which have been noted are yellow vision, sweating of the head and trunk, and in one case albuminuria. It is therefore advisable that the applications should not be made more frequently than once in from seven to fourteen days.[2]

In veterinary practice Kalium Dichromimum, bichromate of

[1] C. Binz, 'Arch. f. path. Anat.,' 1888, Bd. cxiii, S. 1, and 1889, Bd. cxviii, S. 121; Eichhoff, 'Monatshefte f. pr. Dermatol.,' 1889, Bd. viii, No. 1; 1890, Bd. x, No. 5; J. Fabry, 'Arch. f. Dermatol. u. Syph.,' 1889, Bd. xxi, S. 203.

[2] 'Medicinalabteilung des preuss. Kriegsministeriums. Militärärztl. Zeitschr.,' 1890, S. 239; 'ref. Cbl. f. Chirurgie,' 1891, S. 266.

potassium, $K_2C_2O_7$, is used as a cutaneous irritant. It consists of large, deep orange crystals, which are soluble in 10 parts of water.

ACIDUM LACTICUM, lactic acid, $C_3H_6O_3$, also called Ethylidene-lactic acid, $CH_3.CH(OH).COOH$, is produced by the fermentation of sugar and other carbo-hydrates. The officinal preparation contains about 25 per cent. of water. It is a clear, syrupy, odourless liquid, colourless or faintly tinged with yellow, and has an intensely acid taste. It mixes readily with water, alcohol, or ether, and is specially recommended for inhalation in order to dissolve croupy or diphtheritic membranes; from 15 to 20 drops in 15 grammes (about 4 oz.) of water to be inhaled in the form of spray every half-hour. An interesting fact is its employment to destroy tubercle bacilli; when used for this purpose it is said to have little or no effect on the healthy tissues.[1]

ACIDUM NITRICUM FUMANS.—This is used to destroy warts and other cutaneous growths. It is a clear, reddish-brown liquid, which gives off suffocating, orange-coloured fumes. It consists of concentrated nitric acid and nitrogen tetroxide, NO_2, to which the red fumes are due.

ACIDUM TRICHLORACETICUM, trichloracetic acid, $C_2Cl_3HO_2$, or $CCl_3.COOH$, is a colourless, deliquescent, crystalline substance. It has a faint pungent odour and a strong acid reaction, and is soluble in water, alcohol, and ether. It is a product derived from acetic acid by the substitution of chlorine for hydrogen, and was first recommended as a caustic remedy in 1868.[2]

The two caustics above mentioned are the most powerful we have. Their efficacy is due to their energetic and rapid oxidising action.

Trichloracetic acid has the advantage of not acting so

[1] v. Mosetig-Moorhof, "Milchsäure als Zerstörungsmittel pathogener Gewebe," 'Cbl. f. Chirurgie,' 1885, S. 193; H. Krause, "Milchsäure gegen Larynxtuberculose," 'Berl. klin. Wochenschr.,' 1885, S. 462.

[2] C. Binz and A. Urner, in the latter's thesis for the degree of Doctor, Bonn, 1868, "Die Chloressigsäure als Aetzmittel;" H. A. Ehrmann, "Ueber die Anwendung und Wirkung des Acidum trichloraceticum bei den Krankheiten der Nase und des Rachens," 'Münch. med. Wochenschr.,' 1890, S. 159.

strongly upon the parts surrounding the cauterised spot, and also of giving comparatively little pain. It may be diluted with water, to any extent, without undergoing decomposition, which is not the case with fuming nitric acid. The addition of water converts the nitrogen tetroxide into nitrogen dioxide and nitrous acid:

$$H_2O + 2NO_2 = NO + 2HNO_2,$$

with the evolution of red fumes; the fluid turns first green, then blue, and finally, as only nitric acid and water are left, becomes colourless. The green and blue colour are due to the solution of the nitrous oxide in the nitric acid. The former, as I have already demonstrated, is very readily decomposed. In water it disintegrates, forming nitrogen dioxide and nitric acid.

Kali Causticum fusum, or potassium hydrate, KOH, a dry white substance, not easily broken and very deliquescent. This preparation, which is usually moulded into little sticks, is one of the most rapid and powerful of caustic remedies. It penetrates to a considerable depth, but unfortunately destroys a larger area than that to which it is primarily applied. Solution of caustic potash, Liquor Kali Caustici, or Liquor Potassæ, containing 15 per cent. of KOH, is used for baths, washes, and injections (100 to 300 grammes being added to a full length bath). The action of Kalium Carbonicum, carbonate of potash, K_2CO_3, is similar, though not so strong. This is a white salt having an alkaline reaction, and entirely dissolving in an equal weight of water. The aqueous solution, Liquor Kalii Carbonici, in 3 parts, contains one part of the salt.

Liquor Natri Caustici, solution of caustic soda, containing 15 per cent. of NaOH, is used for the same purposes as caustic potash, and resembles it in outward effect, but is milder in its action.

Calcarea Usta, quicklime or calcium oxide, CaO, is a dense white substance, which, moistened with half its weight of water, becomes very hot and disintegrates, and on the addition of more water forms a smooth paste. A mixture of equal parts of quicklime and caustic potash forms Vienna paste, a caustic which acts slowly and to a limited extent,

and is comparatively painless. It may be used for opening abscesses in patients who are afraid of the knife.

SAPO KALINUS, or potash soap, is used for certain special purposes, and may be included in the present group. It is prepared by heating together solution of caustic potash and linseed oil in a steam-bath. It is a brownish-yellow, transparent substance, soft and unctuous, has a faint soap-like odour, and is soluble in water and alcohol. It has been employed with good results as a liniment to promote the absorption of chronic glandular swellings, and also of pericardial and peritoneal exudations.[1] How it acts I cannot say. To cover its unpleasant odour, ½ per cent. of some fragrant ethereal oil may be added to it. A piece the size of a walnut is rubbed into the skin near to the seat of the disease, three or four times a day.

A mixture of potash soap with a fifth part of fresh mustard powder, applied from time to time, is used as a remedy for lymphoma, under the name of Kern's cataplasm.[2]

SAPO KALINUS VENALIS, soft soap, is also included in the German Pharmacopœia, as it is employed in medicine, particularly in veterinary science, and the commercial article is very often impure and adulterated.

The following salts are also officinal, and are employed as caustics:

ARGENTUM NITRICUM CUM KALI NITRICO, nitrate of silver and potassium. This is prepared by fusing one part of nitrate of silver with two of nitrate of potassium. The action of this preparation is milder than that of pure nitrate of silver.

CUPRUM SULPHURICUM, Cupri Sulphas, sulphate of copper, consists of transparent blue crystals, which effloresce slightly in dry air, and are soluble in 3·5 parts of water, but insoluble in alcohol. As a caustic, it is employed chiefly for ophthalmic purposes.

Sulphate of copper was also used formerly as an emetic,

[1] Kapesser, 'Berl. klin. Wochenschr.,' 1878, S. 73; Senator, ibid., 1882, S. 573; Kormann, 'Veroffentl. d. Ges. f. Heilk. in Berlin,' 1881, Bd. iv, S. 8.

[2] Busch, W., Bonn, 'Sitzungsber. d. Niederrhein. Ges. f. Natur. und Heilk.,' 1880, S. 292.

but as such its use is superfluous; it does not act any better than tartar emetic, nor more rapidly than apomorphine, and it is highly corrosive. The German Pharmacopœia fixes the maximum dose at 1 gramme (15 grains).

Cuprum Aluminatum, or lapis divinus, copper alum, is prepared by fusing together copper sulphate, potassium nitrate, alum, and powdered camphor; it is a gentle caustic, and is used chiefly in ophthalmic disorders. It is in the form of bright blue-green lumps or rods, which, with the exception of a slight sediment, are soluble in 16 parts of water.

Zincum Chloratum, Zinci Chloridum, chloride of zinc, $ZnCl_2$, consists of white powder or of opaque rods, which are very deliquescent, and dissolve almost entirely in alcohol and water. When heated it liquefies, and then volatilises in the form of white fumes, leaving a residue which, while hot, has a yellow colour. The aqueous solution has an acid reaction. At one time it was used as a caustic, being made into a paste with flour and similar substances in various proportions. A layer of suitable thickness was then applied to ulcers, &c., and allowed to remain on the part for several days. In recent times it has been employed as an antiseptic in the treatment of wounds. After an operation the wound is covered with a mixture of 5 parts of chloride of zinc, 50 of oxide of zinc, and 50 of water, and then heals[1] without any suppuration taking place.

[1] W. v. Noorden, P. Bruns' 'Beiträge z. klin. Chir.,' 1889.

XXXI.

Officinal substances which are used in the preparation of pills, and for surgical and other purposes—Concluding remarks upon the methods employed in scientific investigations.

IT now only remains to consider briefly certain officinal preparations which are used for mechanical purposes, and in the first place we will discuss one which is used chiefly to improve the flavour of remedies.

RADIX LIQUIRITIÆ or liquorice root. The root or underground stem—scraped, but otherwise in a natural state—of the Russian variety of *Glycyrrhiza glabra* (*G. glandulifera*), a papilionaceous plant. The chief constituent is a sweet substance, Glycyrrhizin, $C_{44}H_{63}NO_{18}$, a brown amorphous powder, which is a tribasic acid, and in the root is combined with lime and ammonia. If boiled with diluted acids it is converted into para-saccharic acid, $C_6H_{10}O_8$, and Glycyrrhetin, the latter being a neutral, crystalline substance.

The preparation obtained from the root is SUCCUS LIQUIRITIÆ, or extract of liquorice. This is prepared by boiling, straining and pressing the root, and evaporating the liquid to a suitable consistence. It is made up in the form of glossy black sticks or lumps, which have a very sweet taste, and are not entirely soluble in water. If the root is macerated with cold water and the liquid evaporated down, a thick brown extract is obtained, which forms a clear solution with water, and is named SUCCUS LIQUIRITIÆ DEPURATUS, or purified liquorice.

Other officinal preparations of the root are ELIXIR E SUCCO LIQUIRITIÆ, which is a brown liquid consisting of 1 part of Succus Liquiritiæ Depuratus, mixed with 3 of Aqua Fœniculi and 1 of Liquor Ammonii Anisatus. It is given in doses of a teaspoonful in inflamed conditions of the upper air-passages. SIRUPUS LIQUIRITIÆ, syrup of liquorice, is prepared by making

an extract of the liquorice root with ammoniated water, evaporating the liquid, and adding sugar.

Purified liquorice is frequently used as a vehicle for pills, as is also the following.

EXTRACTUM TARAXACI, extract of dandelion, a thick brown extract, prepared with cold water, of the root and leaves of *Taraxacum officinale*, one of the Compositæ. The extract is entirely soluble in water, and forms a clear solution.

SAPO MEDICATUS, or medicated soap (see vol. ii, p. 24). This, moistened with water or alcohol, is a good vehicle for pills. SPIRITUS SAPONATUS is the name of a clear, yellow liquid which has an alkaline reaction, and if agitated with water produces abundant froth. It is obtained by saponifying olive oil with solution of caustic potash, and dissolving the olein, &c., in alcohol and water. Mixed with lead plaster, wax, and some camphorated olive oil, medicated soap forms EMPLASTUM SAPONATRUM, a yellowish-white plaster.

TRAGACANTHA, tragacanth, the dried gum obtained from the small stems of various species of Astragalus, indigenous to Asia Minor and south-western Asia. It consists of flaky pieces, which are thin and more or less curved, and swell up into a jelly in water. One part of powdered tragacanth dissolved in 50 parts of water yields a turbid, viscid, insipid mucilage. It is used for the preparation of pills, pastilles and emulsions, and is also a constituent of glycerine ointment.

BOLUS ALBA serves as a neutral vehicle for metallic salts which readily decompose (see vol. ii, p. 187).

ARGENTUM FOLIATUM, silver leaf, is a thin, delicate leaf of pure silver, and is used as a coating for pills, to prevent evaporation, as a precaution against damp, and to improve their appearance.

KERATINUM, keratin. This consists of a brownish-yellow powder or of small transparent scales of the same colour, without taste or smell, but giving out an odour of burnt horn when heated; it is insoluble in the ordinary solvents, and in dilute acids, but soluble in alkalies, ammonia, and concentrated acetic acid. Keratin is prepared from horn shavings. The shavings are first treated with alcohol and ether to free them from fat, and then with pepsin and hydrochloric acid

to get rid of all soluble matter. The residue consequently is unaffected by the gastric secretions, and pills coated with it are not dissolved until acted upon by the alkaline secretions of the small intestines (P. Unna).

When used for coating pills, keratin is first dissolved in ammonia or acetic acid, the pills are then well moistened with the solution, and the solvent afterwards allowed to evaporate.

Saccharum and Mel Depuratum may also be included here. The former is cane or beetroot sugar, $C_{12}H_{22}O_{11}$, which dissolves completely in half its weight of water, and forms a colourless, scentless and sweet-tasting syrup which is miscible in all proportions with alcohol. Aqueous and alcoholic solutions of sugar should not change the colour of litmus paper, and on the addition to them of nitrate of silver or nitrate of barium, there should be scarcely any cloudiness—that is, they should contain not more than traces of chlorides and sulphates.

Sirupus simplex. A white syrup, made of 3 parts of sugar and 2 of water. Sirupus cerasorum, cherry-syrup, made of sour black cherries, crushed with sugar and simple syrup. By repeatedly agitating the syrup, and then letting it stand, the portion which is insoluble in alcohol settles to the bottom. It is of a deep purple-red colour. Sirupus Rubi Idæi, raspberry syrup, prepared in the same way, and of a red colour. These syrups are intended to improve the flavour of various mixtures.

Sirupus Aurantii Corticis, Sirupus Cinnamomi, and Sirupus Menthæ, are also employed for the same purpose. The taste of many unpalatable medicines, however, is rendered still more unpalatable by the addition of sugar.

Mel Depuratum, clarified honey, is a clear syrupy liquid with the peculiar pleasant odour of honey. It is gathered from flowers by the bees, swallowed, and then again discharged into the wax cells (honeycombs). It consists chiefly of invert sugar, a mixture of syrupy levulose, and crystallisable dextrose. It also contains some formic acid, lime and gum, which are almost entirely removed by treating the honey with warm water, filtering, and then evaporating it down. Mixed with an alcoholic infusion of rose-leaves and glycerine, it is called Mel Rosatum, which is

a clear, syrupy liquid containing a trace of otto of roses and a little tannic acid together with the honey.

Crude honey is a popular remedy as a local stimulant, and for antiseptic purposes. Its effect, if any, must be chiefly due to the formic acid, of which it contains about 0·1 per cent. The honey of the Pharmacopœia, deprived of this acid, is neither more irritant nor more antiseptic than a similar quantity of saccharine solution, which however ferments more readily than crude honey, and is more expensive. The conclusion to be drawn from this is that there is no advantage in using purified honey, and that simple syrup serves precisely the same purpose.

With the next preparation we pass on to the group of substances which are chiefly used for surgical dressings.

Amylum Tritici, wheaten starch. A very fine white powder which, placed in water and magnified 150 times, is seen to consist of granules of almost circular form, some very small, and others, which are fewer in number, much larger; medium-sized granules are rare. On the addition of alcohol the large granules appear to be lenticular or plano-convex. Under the microscope, any intermixture of the irregular and much larger granules of potato starch can easily be recognised. Boiled with 50 parts of water and then allowed to cool, wheaten starch forms a thin, turbid, glutinous liquid, which has neither taste nor smell, and does not affect the colour of litmus paper.

Starch is used as a vehicle for powders, as an ingredient of ointments, enemas, and dusting-powders, and for starch bandages, &c.

Gossypium Depuratum, purified cotton wool, practically $(C_6H_{10}O_5)_x$; the white hairs of the seeds of *Gossypium herbaceum*, *G. arboreum*, and other species, from which fatty matter and all foreign impurities have been removed. If moistened with boiling water, it should not change the colour of litmus paper; if thrown into water it should immediately become saturated and sink. On ignition it should not leave more than 0·3 per cent. of ash, the rest being pure cellulose. It is used as a dressing, either by itself or impregnated with various remedies, and is also the basis of the following preparation.

Collodium, a syrupy liquid, colourless or only faintly tinged with yellow, and of neutral reaction, which dries rapidly on the skin and leaves a thin, transparent and firmly coherent film. It is prepared by immersing purified cotton wool in a mixture of nitric acid and sulphuric acid until it is thoroughly wetted, then washing it and dissolving 1 part in 21 parts of ether and 3 of rectified spirit. The collodion wool (colloxylin) obtained in the first stage of this process is akin to gun-cotton (pyroxylin). If $C_6H_{10}O_5$ be taken as the formula of cellulose, then gun-cotton is $C_6H_5(O.NO_2)_5$, that is, cellulose pentanitrate; it is highly explosive, and does not dissolve in spirit of ether. The proportion of nitric acid in the mixture used in preparing gun-cotton is larger than that used in making collodion wool. The latter consists chiefly of cellulose dinitrate, $C_6H_8O_3(O.NO_2)_2$, together with a small amount of cellulose trinitrate,

$$C_6H_7O_2(O.NO_2)_3.$$

Collodion wool explodes far less readily than gun-cotton, and is soluble in spirit of ether.

The film left by collodion after the ether and alcohol have evaporated, exerts considerable pressure by its contraction, and thus, in mild cases, diminishes the hyperæmia which might give rise to suppuration. It is also useful as a coating for wounds. This coating adheres firmly to the part; it is easily removed by means of acetic ether, which quickly dissolves it.

Collodium Elasticum is a mixture of 94 parts of collodion with 1 part of castor oil and 5 parts of Canada balsam. It covers but does not constrict the part.

Collodium Cantharidatum is made with ether in which powdered cantharides have been digested, and it consequently contains cantharidin. It serves as a blistering plaster which the patient cannot readily remove. It has an olive-green colour, but in other respects resembles simple collodion.

Calcium Sulphuricum Ustum, calcined gypsum, plaster of Paris, $CaSO_4$, is a white amorphous powder which should solidify or set within five minutes, after being mixed with half its own weight of water.

Sulphate of lime, as it occurs in nature, contains 2 mole-

cules of water of crystallisation, which by the application of heat may be almost entirely driven off, and the sulphate in this way reduced to a powdered state. If mixed with water the latter is rapidly absorbed, a certain amount of heat is developed, and the gypsum again solidifies. If gypsum containing water of crystallisation is too strongly heated, it will subsequently absorb water very slowly and is unfit for use. Samples also should be rejected which, though originally good, have become damp from keeping or other causes, as they will not solidify properly on the further addition of water.

LIQUOR NATRII SILICICI, liquid glass, or solution of sodium silicate, the composition of which is approximately

$$Na_2SiO_3 + 2SiO_2 + \text{water},$$

is a clear, colourless or faintly yellow liquid with an alkaline reaction, and gives a gelatinous precipitate on the addition of acids. It specific gravity is 1·3 to 1·4. It is obtained by dissolving finely powdered silicic acid in a hot solution of caustic soda, or by fusing a mixture of 45 parts of quartz sand with 23 parts of anhydrous soda and 3 of powdered charcoal. It is used as a surgical dressing.

GUTTA PERCHA is the concrete juice of certain trees growing in the East Indies, especially in Ceylon and the southern parts of the Malay Peninsula, chiefly members of the genera Dichopsis, Isonandra, and Payena, belonging to the Nat. Ord. Sapotacea. It consists of pieces of a dark brown colour which, when immersed in hot water, become soft and pliable, but harden again as they get cold. Gutta percha is almost entirely soluble in warm chloroform. PERCHA LAMELLATA, gutta-percha tissue, is made by rolling out purified gutta percha into very thin layers. It is of a reddish-brown colour, translucent, and not adhesive. Gutta percha is chiefly composed of the hydrocarbon $C_{20}H_{32}$, together with the products derived from the oxidation of that substance.

EMPLASTRUM ADHÆSIVUM, adhesive plaster. This is prepared by melting 100 parts of lead plaster, and heating it until all the water has evaporated. To this are added 10 parts of yellow wax, dammar resin, and colophony, and 1 part of turpentine balsam. The plaster has a brownish-yellow colour, and is very adhesive. The resin above mentioned,

Resina Dammar, is obtained from *Dammara alba* (*Agathis alba*), *D. orientalis*, *Hopea micrantha*, *H. splendida*, and other South American trees. It consists of yellowish-white transparent drops, pieces, or lumps, yielding a white inodorous powder which is freely soluble in ether and chloroform, but less readily in alcohol. Dammar resin is more easily softened than other kinds by the warmth of the skin.

Colophonium, colophony or common resin, is the resin which is left after the distillation of crude turpentine; a brittle yellow or light brown substance, which dissolvês slowly in equal parts of alcohol, and gradually deposits, as it cools, crystals of abietinic acid, $C_{44}H_{64}O_5$, of the anhydride of which, $C_{44}H_{62}O_4$, colophonium is chiefly composed.

Fungus Chirurgorum, touchwood or surgeon's agaric. This consists of extremely soft and light layers of tissue of a beautiful brown colour, which are cut from the *Polyporus fomentarius*, a sessile fungus infesting the trunks of old oaks and beeches. When examined under the microscope surgeon's agaric is seen to consist simply of filiform cells. It readily absorbs twice its own weight of water, and on squeezing the latter out and evaporating to dryness very little residue should be left. Touch-wood which, by being soaked in a solution of nitre or other salts, has been converted into German tinder, must be avoided. Surgeon's agaric is used to check superficial capillary hæmorrhage. If pressed into the bleeding parts, the filiform cells swell up and plug the vessels.

Hirudines, leeches; *Sanguisuga medicinalis* and *officinalis* (Annulata). The former are obtained chiefly from the marshes of Northern Europe, the latter from those of the south of Europe, and are from 1 to 5 grammes in weight. The amount of blood extracted by them and that which flows spontaneously after their removal from the part, varies very much according to the size of the leech and the length of time the subsequent bleeding continues. With a large leech the average quantity may be reckoned at 12 grammes (3 drachms). The blood is extracted from the cutaneous capillaries by the leech applying its suctorial tube, at the bottom of which is the triangular oval aperture with its

three rows of teeth. With these it bores through the skin. It then creates a vacuum by alternately expanding and contracting its muscular throat. The chief result of the bleeding is to relieve the retarded circulation in, and the congested condition of the neighbouring capillaries, and so to prevent any considerable emigration of leucocytes,—in other words, to prevent the formation of pus.

It is frequently a difficult matter to stop the bleeding resulting from leech-bites, and the blood they swallow does not usually coagulate, even after they have discharged it. The reason[1] of this is that a fluid is secreted in the mouth of the leech, which prevents the blood coagulating, but without causing any other perceptible alteration in it.

Some years ago a young lady in Paris attempted suicide by inducing free hæmorrhage with a number of leeches. Having bought fifty of them, she undressed completely and applied them to her body from the knees to the breast. The creatures, having satiated themselves, dropped off, but the bites continued to bleed. The room was covered with blood, the odour of which penetrated outside. The door was opened and the lady was found lying on the floor in a deep swoon. She was removed to a hospital, and slowly recovered.

[1] J. B. Haycraft, 'Arch. f. exper. Path. u. Pharmak.,' 1884, Bd. xviii, S. 209. With regard to the use of leeches in olden times, see Ch. Huber, 'Arch. f. klin. Med.,' 1891, Bd. xlviii, S. 522.

CONCLUSION.

We have now completed our scientific review of the substances included in the Pharmacopœia. At the commencement I indicated to you what are the objects and aims of pharmacology; I will now, in conclusion, direct your attention to the methods by which those objects may be attained.

The first question which arises is whether, in our scientific investigations, the benefit and cure of the patient are to be regarded as our special objects, or whether, leaving him out of the question, we seek only to discover what results are produced in the living organism, and especially in the animal organism, by certain substances which act chemically, without reference to any therapeutic effects which such substances may have.

It seems to me that investigations of both kinds should be made, and that the one kind should not exclude the other. For you who are preparing to enter the medical profession, the former is by far the most interesting and important. To be thoroughly acquainted with the external properties, the actions, the advantages and dangers attendant on the use of officinal remedies is, to the physician, of greater moment than anything else; investigations into the properties of these substances without any reference to their therapeutic application, belong simply to the laboratory. The additional knowledge which is thereby gained has the indisputable value of scientific facts in general; from an educational point of view, it only becomes valuable when it increases our knowledge of the actions of remedies, or when it becomes practically useful in the treatment of disease.

Now, it has been supposed that the actions of remedies could best be learned from their effects upon man himself, and especially from their effects upon healthy men. A few examples will show that this is not the case. We cure

malarial fever with quinine, but not one of all the subjective symptoms induced in human beings, by large or small doses of quinine, has the slightest connection with its curative action. This we have learned from experience; we could not have discovered it by experimenting with quinine on healthy subjects, neither would such experiments enable us in any way to understand it. The cure of acute rheumatism by salicylic acid, of syphilis by iodine and mercury, are other cases in point. We know, too, how little pharmacological science was advanced by the self-sacrificing experiments of Jörg and his pupils, with digitalis, iodine, hydrocyanic acid, camphor, &c., in 1825.

Another fact which must be taken into consideration, is that the administration to healthy persons of non-poisonous substances, in doses which would be very efficacious if given to a man suffering from disease, often produce absolutely no effect. The 2 grammes (30 grains) of iodide of potassium, which will mitigate or remove the nocturnal pains in the bones of a syphilitic patient, have no more effect upon a healthy individual than the same quantity of common salt. At most, all kinds of imaginary sensations are produced (as was the case with S. Hahnemann and his successors), which are erroneously attributed to the drug that has been taken. And if the substances taken are recognised poisons, the imagination becomes livelier still. Numerous symptoms arise in various parts of the body, and combining with those produced by the genuine action of the remedy, create a medley of worthless impressions, the nature of which can only be the subject of arbitrary speculation.

Our aims and purposes are promoted by the study of such cases of disease as present the characteristics of an involuntary experiment. Cases of poisoning, where the precise cause is known, and when the resulting symptoms are distinct and manifest, are examples of this kind, and from them we may arrive at conclusions bearing upon the therapeutic employment of the drug, and may obtain suggestions for useful experiments upon animals. I here call to remembrance such instances as the case of poisoning with coffee, reported by Curschmann; the instructive account of the post-mortem appearances in a case of poisoning by chlorate of potassium

given by Marchand; the case of poisoning from santonin which came under my own observation, with many others of a similar nature.

A HUMAN BEING WHO IS SUFFERING FROM DISEASE, cannot, in any way, be regarded as a fit subject for experimental investigations. It is only when certain essential conditions, which I shall presently enumerate, have been absolutely satisfied that any idea of the kind can be entertained. Then, of course, he is often the first to benefit by the experiment, while at the same time the question, to a large extent, is solved.

HEALTHY ANIMALS are incomparably better suited for this purpose than man. What can be accomplished by means of digitalis, caffeine, atropine, the new hypnotic remedies, &c., may in many cases be demonstrated with certainty upon them, and the action of these remedies can then be tried on human beings; though, even here, we are restricted by certain conditions, for the action of chemical compounds on animals is in many ways very different from their action on man. If, for example, we were to draw conclusions as to the action of atropine and morphine upon the human subject, from the extraordinary tolerance of these remedies by rabbits, we should find ourselves greatly mistaken; on the other hand, we should also be in error if, after testing the action of chloroform upon dogs, we supposed that it produced equally dangerous effects on man. Moreover, individual species of animals differ widely in the way in which they are affected by poisons. Chloroform is, for example, a good and harmless narcotic for horses; it quickly kills ruminants, dogs, and cats. Ether as a narcotic is very readily tolerated by cats, but very badly by sheep. Morphine is generally a sedative for dogs; it is a powerful stimulant for horses and cattle. The ox is extremely susceptible to mercury, the horse to tartar emetic and croton oil, the cat to carbolic acid.[1] We might go so far as to compile a "Comparative Toxicology," which would show, among other things, a marked difference in the action of the same chemical compound upon *Rana temporaria* and *Rana esculenta*.[2]

[1] Fröhner, 'Monatshefte f. prakt. Tierheilkunde,' 1895, Bd. vi.

[2] Schmiedeberg, 'Arch. f. exper. Path. u. Pharmak,' 1874, Bd. ii, S. 62.

From the study of DISEASE IN ANIMALS, much instruction may be gained; I need only remind you of the numerous experiments on the artificial production of fever and its treatment; upon diabetes artificially induced and its restriction; on the treatment of disease of the bones by phosphorus; on the antagonistic action of poisons, as for instance the effect of atropine in averting fatal paralysis; and on the efficacy of the mild ethereal oils in lessening violent irritation of the nervous centres. But, on the whole, we work within narrow limits, for most of the typical diseases to which human beings are liable, cannot be induced in animals. Consequently in these cases, all questions as to the therapeutic effects of remedies are left unanswered by experiments made on animals.

Some of the results hitherto obtained by experimenting upon healthy and diseased animals are simply valueless, because the experiments were carried out in too complicated a fashion, or because the conditions under which they were performed, do not correspond with those which occur in the human subject. Results of an entirely different character can be produced with the same poison or medicine, and upon animals of the same species, according to the way in which the experiment is conducted. This is not the place to go into details or prove my statement by published examples, numerous as such examples are; I have already, several times, been obliged to do this in my own defence.[1] But I do not thereby mean to assert that complicated and violent methods, such, for instance, as directly injecting a remedy into a blood-vessel, are superfluous. They are at times absolutely necessary in order to determine the general action of new substances. But they should not be regarded as a matter of routine, nor should they be used when simple experiments would answer equally well. The results obtained by such active measures cannot be very readily utilised, and in no case should they be directly applied to the human subject without further confirmation.

By investigating the purely CHEMICAL PROPERTIES and ELE-

[1] Cf. *inter alia* 'Deutsche med. Wochenschr.,' 1879, S. 615 und 627; 1880, S. 149; 'Berliner klin. Wochenschr.,' 1896, No. 40, "Die Wirkung übergrosser Gaben Atropin auf die Athmung."

MENTARY ACTION of a Pharmakon[1] we may sometimes learn more of its character and of the nature of its effect upon human beings, than by testing its action on the living organism. From the action of iodoform in a solution of fatty oil, and from the action of the iodine which is therein liberated,[2] important conclusions have been reached respecting the action of iodoform in the human body; our knowledge of the way in which quinine acts in malarial fevers was obtained by studying its effect on the lowest organisms; the striking benefit resulting from the use of cod-liver oil is rendered intelligible by experiments on the easiest way of producing a fine emulsion of nutritive fat; the antipyretic virtue of salicylic acid was inferred from the discovery of its antiseptic properties, its non-poisonous nature, and its partial indestructibility in the organism; the discovery of the presence of BOTH arsenious and arsenic acids, after either had been mixed with fresh protoplasm, led to further experiments being made upon living animals, and to sundry conclusions being formed with regard to the action of arsenic on the system.[3] The results of such investigations have just as much weight, as the determination of the blood-pressure, or the gaseous interchange in the living animal, has in solving other questions.

We may also here refer to the additional knowledge which has been gained by studying the changes which remedies undergo within the body. This may lead to the detection, in some remedies, of pharmaco-dynamic properties which have not as yet been noted, and to a better interpretation of the actions of some of those remedies which we are already in the habit of using. Take salicin as an example. It is chemically and physiologically a neutral body, but when introduced into the living organism it becomes active in both respects, owing to the fact that salicylic acid is then liberated from it. Take, again, ordinary ethyl alcohol. In the cells it is oxidised and converted into carbonic acid and water, but the intermediate stages of this oxidation,

[1] See Vol. I, p. 2.
[2] See Vol. I, p. 174.
[3] C. Binz, 'Archiv f. exper. Path. u. Pharmak.,' 1895, Bd. xxxvi, S. 275, und 1896, Bd. xxxviii, S. 259.

the formation of aldehyde and acetic acid, are by no means unimportant as regards the life of those cells in the immediate proximity of which these products are formed. It is quite conceivable that a chief part of the effect is produced by these intermediate products, and not by the unoxidised molecule $C_2H_5.OH$. In many instances, no doubt, it has been found after careful investigation that the changes which a remedy undergoes in the system have little to do with its medicinal action; but the contrary is unquestionably often the case, and the subject is therefore one worthy of attention.

A wide field has been opened out, and a great impulse has been given to pharmacological research by the STUDY OF THE LOWEST ORGANISMS AS THE EXCITING CAUSES OF DISEASE. These organisms and their products will now have continuous attention bestowed upon them and will be the subjects of systematic exhaustive investigations, especially as regards the way in which they may be influenced and modified by the action of chemical substances. Any one, however, who from such inquiries expects definite results which can be immediately turned to account, has little knowledge of the narrow and intricate paths which, in every science, have to be traversed in order to bring theoretical views into actual practice. Here especially we are hampered by the difficulty previously referred to, that in the body we have not to deal, as in the glass tube or under the microscope, with chemical substances of a simple and definite character, but with the products of their decomposition, oxidation, reduction, and combination, about which at present we know very little.

If, then, to return to the question of experiments upon HUMAN BEINGS, a certain chemical substance in certain doses has been proved to have no poisonous effects upon animals; if its effects upon them are distinctly analogous to therapeutic processes in human beings; if, when administered with care, there seems nothing to justify the suspicion that it may be poisonous to human beings; or if the substance from which it is derived has proved useful as a popular remedy; if, finally, the existing methods and remedies are in any or in every respect defective; then—beginning with the smallest dose—it is not only lawful but it is imperative that

the patient should be experimented upon, both in his own interests and for the advancement of science. Had the contrary opinion been held in former times, suffering humanity would not have benefited in the slightest degree by the valuable discoveries of the last fifty years; and if we are unwilling that our clinical teachers and hospital physicians should still continue researches of this kind, we should have to be content with the knowledge—absolutely insufficient for therapeutic purposes—which has been obtained by interrogating nature and by chemical research; and should be unable for all time, to acquire and utilise such knowledge as there is still to be gained from researches of this character. The introduction into practice of such remedies as chloroform, bromide of potassium, iodoform, pilocarpin, carbolic acid, antipyrin, cocaine, &c., illustrates and strongly supports the views here put forward.

Finally, as I have previously suggested, let us, as of old, be still guided by CLINICAL EXPERIENCE. Facts have thereby been established which have outlived all sorts of theoretical views; it has not infrequently happened that modern investigations into the actions and properties of remedies which had gradually fallen into disuse, have justified the grounds on which these remedies were formerly employed. In illustration of this I need only refer to the discovery of arbutin in bearberry-leaves, of salicin in willow bark, and of agaricin in larch fungus. We can hardly assume that the knowledge already attained in this direction is altogether exhausted. Clinical experience has very often furnished a correct judgment without the assistance of any control experiments on animals. Brown, the founder of the Brunonian theory, Kirchgässer, Todd,[1] and others had observed that alcohol was beneficial in febrile conditions, long before it was possible for me and my pupils, with the aid of a thermometer,

[1] They, however, were not the first to do so, in proof of which I need only mention the work of Dr. M. Tirellus, 'De historia vini et febrium libri duo, quorum in primo agitur de vino simpliciter, in altero vero de febribus in vini gratiam; demonstraturque potissimum quibuslibet febribus et quolibet tempore propinatum salutare,' Venice, 1630, 395 pp., 4to.

to study its action and watch its effect upon animals suffering from fever, and so to arrive at a scientific basis for the employment of alcohol in other forms of disease; and it was owing to the statements made by those clinical observers that the experimental investigation of the subject was undertaken. This is but one example out of many in which experience has been the teacher, and has led the way to investigations which have been attended with highly profitable results.

It follows, then, that the study of therapeutics should not be pursued simply on the one side. Particular individuals may devote themselves to one special part of the subject, and this may be advantageous so far as the division of labour is concerned, and also for the attainment of individual proficiency in research and technical dexterity. But our knowledge of the subject in its entirety can only be enlarged by utilising to the fullest extent, and according to scientific principles, the various methods of investigation to which I have just now referred.

TABLE

from the German Pharmacopœia, showing the MAXIMUM DOSE *of certain remedies which, under ordinary circumstances, may be administered to an adult.*

In Germany, when any of the following remedies are prescribed for internal administration, the Apothecary or Chemist must not dispense a larger dose than that here given, unless the Physician indicates on the prescription, by a special mark (!), that a larger quantity has been intentionally prescribed.

	Largest single dose.		Largest quantity to be given in 24 hours.	
	Grammes.	Grains.	Grammes.	Grains.
Acetanilidum	0·5	7½	4·0	60
Acidum Arsenicosum	0·005	$\frac{1}{13}$	0·02	⅓
Acidum Carbolicum	0·1	1½	0·5	7½
Agaricinum	0·1	1½	—	—
Amylenum Hydratum	4·0	60	8·0	120
Apomorphinum Hydrochloricum ...	0·02	$\frac{3}{10}$	0·1	1½
Aqua Amydalarum Amarum ...	2·0	30	8·0	120
Argentum Nitricum	0·03	$\frac{9}{20}$	0·2	3
Atropinum Sulphuricum	0·001	$\frac{1}{60}$	0·003	$\frac{1}{20}$
Auro-Natrium Chloratum	0·05	¾	0·2	3
Cantharides	0·05	¾	0·15	2¼
Chloralum Formamidatum	4·0	60	8·0	120
Chloralum Hydratum	3·0	45	6·0	90
Chloroformium	0·5	7½	1·0	15
Cocainum Hydrochloricum	0·05	¾	0·15	2¼
Codeinum Phosphoricum	0·1	1½	0·4	6
Coffeinum	0·5	7½	1·5	22
Cuprum Sulphuricum	1·0	15	—	—
Extractum Belladonnæ	0·05	¾	0·2	3
Extractum Colocynthidis	0·05	¾	0·2	3
Extractum Hyoscyami	0·2	3	1·0	15
Extractum Opii	0·15	2¼	0·5	7
Extractum Strychni	0·05	¾	0·15	2¼
Folia Belladonnæ	0·2	3	1·0	15
Folia Digitalis...	0·2	3	1·0	15
Folia Stramonii	0·2	3	1·0	15
Fructus Colocynthidis	0·5	7½	1·5	22

	Largest single dose.		Largest quantity to be given in 24 hours.	
	Grammes.	Grains.	Grammes.	Grains.
Gutti (Cambogia)	0·5	$7\frac{1}{2}$	1·0	15
Herba Conii	0·5	$7\frac{1}{2}$	2·0	30
Herba Hyoscyami	0·5	$7\frac{1}{2}$	1·5	22
Homatropinum Hydrobromicum ...	0·001	$\frac{1}{60}$	0·003	$\frac{1}{20}$
Hydrargyrum Bichloratum	0.02	$\frac{3}{10}$	0·1	$1\frac{1}{2}$
Hydrargyrum Bijodatum	0·02	$\frac{3}{10}$	0·1	$1\frac{1}{2}$
Hydrargyrum Cyanatum	0·02	$\frac{3}{10}$	0·1	$1\frac{1}{2}$
Hydrargyrum Oxydatum	0·02	$\frac{3}{10}$	0·1	$1\frac{1}{2}$
Hydrargyrum Oxydatum via humida paratum	0·02	$\frac{3}{10}$	0·1	$1\frac{1}{2}$
Hyoscinum Hydrobromicum ...	0·0005	$\frac{1}{130}$	0·002	$\frac{1}{33}$
Jodoformium	0·2	3	1·0	15
Jodum	0·05	$\frac{3}{4}$	0·2	3
Kreosotum	0·2	3	1·0	15
Liquor Kalii Arsenicosi	0·5	$7\frac{1}{2}$	2·0	30
Morphinum Hydrochloricum ...	0·03	$\frac{9}{20}$	0·1	$1\frac{1}{2}$
Oleum Crotonis	0·05	$\frac{3}{4}$	0·1	$1\frac{1}{2}$
Opium	0·15	$2\frac{1}{4}$	0·5	$7\frac{1}{2}$
Paraldehydum	5·0	75	10·0	150
Phenacetinum	1·0	15	5·0	75
Phosphorus	0·001	$\frac{1}{60}$	0·005	$\frac{1}{12}$
Physostigminum Salicylicum ...	0·001	$\frac{1}{60}$	0·003	$\frac{1}{20}$
Pilocarpinum Hydrochloricum ...	0·02	$\frac{3}{10}$	0·05	$\frac{3}{4}$
Plumbum Aceticum	0·1	$1\frac{1}{2}$	0·5	$7\frac{1}{2}$
Santoninum	0·1	$1\frac{1}{2}$	0·5	$7\frac{1}{2}$
Semen Strychni	0·1	$1\frac{1}{2}$	0·2	3
Strychninum Nitricum	0·01	$\frac{1}{7}$	0·02	$\frac{3}{10}$
Sulphonalum	4·0	60	8·0	120
Tartarus Stibiatus	0·2	3	0·5	$7\frac{1}{2}$
Thallinum Sulphuricum	0·5	$7\frac{1}{2}$	1·5	22
Tinctura Aconiti	0·5	$7\frac{1}{2}$	2·0	30
Tinctura Cantharidum	0·5	$7\frac{1}{2}$	1·5	22
Tinctura Colchici	2·0	30	5·0	75
Tinctura Colocynthidis	1·0	15	5·0	75
Tinctura Digitalis	1·5	22	5·0	75
Tinctura Jodi	0·2	3	1·0	15
Tinctura Lobeliæ	1·0	15	5·0	75
Tinctura Opii Crocata	1·5	22	5·0	75
Tinctura Opii Simplex	1·5	22	5·0	75
Tinctura Strophanthi	0·5	$7\frac{1}{2}$	2·0	30
Tinctura Strychni	1·0	15	2·0	30
Tubera Aconiti	0·1	$1\frac{1}{2}$	0·5	$7\frac{1}{2}$
Veratrinum	0·005	$\frac{1}{13}$	0 02	$\frac{3}{10}$
Vinum Colchici	2·0	30	5·0	75
Zincum Sulphuricum	1·0	15	—	—

INDEX OF REMEDIES.

B.

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P.

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LIST OF AUTHORS REFERRED TO IN THE TEXT.

C.

I.

J.

K.

L.

M.

S.

ERRATA.

Vol. I, page 85, line 5 from bottom, for *Stokois* read *Stokvis*.
„ „ 211, „ 15 „ „ for *power* of the intestines *is*, read *nerves* of the intestines *are*.
„ „ 225, „ 5 „ „ for *iodate* read *hydriodate*.
„ „ 226, „ 7 „ top, for *hydrobromide* read *hydrobromate*.
„ „ 293, „ 16 „ „ for *Dippelin* read *Dippelii*.
„ „ 299, „ 13 „ bottom, for $C_{20}H_{21}N_2O_2$ read $C_{21}H_{22}N_2O_2$.
„ „ 313, „ 7 „ „ for SAPONATA read SAPONATO.
„ „ 313, „ 10 „ „ for AMMONIATA read AMMONATO.
„ „ 378, „ 17 „ top, for *Spinosa* read *Spinosæ*.
„ „ 378, „ 19 „ „ for URETICA read URETICÆ.
Vol. II, „ 9, „ 8 „ bottom, for *Radii* read *Radix*.
„ „ 21, „ 4 „ „ for *Newaschen* read *Lewaschen*.
„ „ 31, „ 6 „ „ for *Magnesia* read *Magnesii*.
„ „ 42, „ 8 „ top, for *Syrupus* Ferri *Iodati* read *Sirupus* Ferri *Jodati*.
„ „ 44, „ 10 „ „ for *Syrupus* read *Sirupus*.
„ „ 72, „ 4 „ „ for *arseniettеd* read *arsenetted*.
„ „ 92, „ 13 „ „ for KALI read KALII.
„ pages 94, 95, 96, for *arsenietted* read *arsenetted*.
„ page 109, line 6 from bottom, for *cetas* read *Acetas*.
„ „ 111, lines 1, 4, 15, 17 from bottom, for *Cerusæ* read *Cerussæ*.
„ „ 139, line 10 from bottom, for *Hydrargyrum* read *Hydrargyri*.
„ „ 140, „ 5 „ top, for GYRUM read GYRI.
„ „ 143, „ 7 „ „ for *Hydrargyrum* Subchloridum read *Hydrargyri* Subchloridum.
„ „ 151, „ 23 „ „ for *Biniodatum* read *Bijodatum*.
„ „ 151, „ 25 „ „ for *Hydrargyrum* read *Hydrargyri*.
„ „ 367, „ 16 „ bottom, for *Malleolus* read *Mallotus*.
„ „ 368, „ 16 „ top, for ARECA read ARECÆ.
„ „ 386, „ 6 „ bottom, for *Rheumatismus* read *Rheumatism*.
„ „ 398, „ 19 „ „ for COCHLEARIA read COCHLEARIÆ.
„ „ 399, „ 3 „ top, for ARNICA read ARNICÆ.
„ „ 405, „ 10 „ bottom, for NATRI read NATRII.

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